



Clinical trial results:

A Phase 2 Study to Evaluate the Efficacy and Tolerability of Debio 1562 in Combination with Rituximab in Patients with Relapsed and/or Refractory Diffuse Large B-Cell Lymphoma and Other Forms of Non-Hodgkin's Lymphoma

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2015-004061-87 |
| Trial protocol | BE HU BG CZ PL IT |
| Global end of trial date | 25 June 2021 |

Results information

| | |
|--------------------------------|---|
| Result version number | v3 (current) |
| This version publication date | 23 June 2024 |
| First version publication date | 09 July 2022 |
| Version creation reason | • Correction of full data set Minor changes required |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | Debio 1562-201 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02564744 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Debiopharm International S.A. |
| Sponsor organisation address | Chemin Messidor 5-7, Lausanne, Switzerland, CH-1006 |
| Public contact | Clinical Department, Debiopharm International S.A., +41 213210111, ClinicalTrials@debiopharm.com |
| Scientific contact | Clinical Department, Debiopharm International S.A., +41 213210111, ClinicalTrials@debiopharm.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 | 25 June 2021 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 25 June 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To determine the safety, tolerability, and anti-tumor activity of the proposed Debio 1562 dose regimens in combination with rituximab.

Protection of trial subjects:

Written approval of the study protocol and the informed consent was obtained from the independent ethics committee (IEC), prior to initiation of the study. The study was conducted in accordance with local regulations, Good Clinical Practice (GCP), International Council for Harmonisation (ICH) notes for GCP (ICH/CPMP/135/95), and ethical principles that have their origin in the Declaration of Helsinki and its amendments.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 05 June 2016 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Belgium: 14 |
| Country: Number of subjects enrolled | Hungary: 8 |
| Country: Number of subjects enrolled | Poland: 7 |
| Country: Number of subjects enrolled | United States: 32 |
| Country: Number of subjects enrolled | Czechia: 10 |
| Country: Number of subjects enrolled | Italy: 7 |
| Country: Number of subjects enrolled | Bulgaria: 7 |
| Country: Number of subjects enrolled | Switzerland: 1 |
| Country: Number of subjects enrolled | Ukraine: 14 |
| Worldwide total number of subjects | 100 |
| EEA total number of subjects | 53 |

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) | 28 |
| From 65 to 84 years | 69 |
| 85 years and over | 3 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 38 investigative sites in the United States, Belgium, Ukraine, the Czech Republic, Hungary, Bulgaria, Italy, Poland, and Switzerland from 05 June 2016 to 25 June 2021.

Pre-assignment

Screening details:

A total of 127 subjects were screened and 100 subjects with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) and other forms of non-Hodgkin's lymphoma (NHL) were enrolled, 37 subjects into Part 1 and 63 subjects into Part 2/3.

Period 1

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

Arms

| | |
|------------------------------|-----------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Part 1: Safety Run-in |

Arm description:

Subjects received Debio 1562 0.7 mg/kg, intravenous (IV) infusion followed by rituximab 375 mg/m² IV infusion, once on Day 1 of 21-day cycles until the study discontinuation criteria were met (until they develop disease progression, death, unacceptable toxicity, withdraw consent, start new anti-lymphoma treatment or the Sponsor terminates the study).

| | |
|--|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Debio 1562 |
| Investigational medicinal product code | |
| Other name | Naratuximab emtansine, IMGN529 |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

0.7 mg/kg IV infusion

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Rituximab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

375 mg/m² IV infusion

| | |
|------------------|------------------|
| Arm title | Part 1: Cohort 1 |
|------------------|------------------|

Arm description:

Subjects with R/R DLBCL received Debio 1562 0.7 mg/kg, IV infusion followed by rituximab 375 mg/m² IV infusion, once on Day 1 of 21-day cycles until the study discontinuation criteria were met (until they develop disease progression, death, unacceptable toxicity, withdraw consent, start new anti-lymphoma treatment or the Sponsor terminates the study).

| | |
|--|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Debio 1562 |
| Investigational medicinal product code | |
| Other name | Naratuximab emtansine, IMGN529 |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

| | |
|---|---------------------------------------|
| Dosage and administration details: | |
| 0.7 mg/kg IV infusion | |
| Investigational medicinal product name | Rituximab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 375 mg/m ² IV infusion | |
| Arm title | Part 1: Cohort 2 |
| Arm description: | |
| Subjects with R/R NHL received Debio 1562 0.7 mg/kg, IV infusion followed by rituximab 375 mg/m ² IV infusion, once on Day 1 of 21-day cycles until the study discontinuation criteria were met (until they develop disease progression, death, unacceptable toxicity, withdraw consent, start new anti-lymphoma treatment or the Sponsor terminates the study). | |
| Arm type | Experimental |
| Investigational medicinal product name | Debio 1562 |
| Investigational medicinal product code | |
| Other name | Naratuximab emtansine, IMGN529 |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 0.7 mg/kg IV infusion | |
| Investigational medicinal product name | Rituximab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 375 mg/m ² IV infusion | |
| Arm title | Part 2/3: Cohort A |
| Arm description: | |
| Subjects with relapsed DLBCL received Debio 1562 0.7 mg/kg, IV infusion followed by rituximab 375 mg/m ² IV infusion, once on Day 1 of a 21-day cycle for at least 6 cycles. | |
| Arm type | Experimental |
| Investigational medicinal product name | Debio 1562 |
| Investigational medicinal product code | |
| Other name | Naratuximab emtansine, IMGN529 |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 0.7 mg/kg IV infusion | |
| Investigational medicinal product name | Rituximab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 375 mg/m ² IV infusion | |
| Arm title | Part 2/3: Cohort B |
| Arm description: | |
| Subjects with relapsed DLBCL received Debio 1562 0.4 mg/kg IV infusion followed by rituximab 375 | |

mg/m² IV infusion on Day 1, then Debio 1562 0.2 mg/kg IV infusion on Days 8 and 15 of a 21-day cycle for at least 6 cycles.

| | |
|--|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Rituximab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

375 mg/m² IV infusion

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Debio 1562 |
| Investigational medicinal product code | |
| Other name | Naratuximab emtansine, IMGN529 |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

0.2 and 0.4 mg/kg IV infusion

| Number of subjects in period 1 | Part 1: Safety Run-in | Part 1: Cohort 1 | Part 1: Cohort 2 |
|--------------------------------|-----------------------|------------------|------------------|
| Started | 17 | 8 | 12 |
| Completed | 5 | 1 | 4 |
| Not completed | 12 | 7 | 8 |
| Subject Withdrew Consent | 1 | 1 | 1 |
| Death | 10 | 5 | 4 |
| Investigator decision | - | - | - |
| Reason not specified | 1 | - | - |
| Lost to follow-up | - | 1 | - |
| End of Study Page Missing | - | - | 3 |

| Number of subjects in period 1 | Part 2/3: Cohort A | Part 2/3: Cohort B |
|--------------------------------|--------------------|--------------------|
| Started | 33 | 30 |
| Completed | 14 | 10 |
| Not completed | 19 | 20 |
| Subject Withdrew Consent | - | 2 |
| Death | 16 | 16 |
| Investigator decision | - | 1 |
| Reason not specified | - | - |
| Lost to follow-up | - | 1 |
| End of Study Page Missing | 3 | - |

Baseline characteristics

Reporting groups

| | |
|---|-----------------------|
| Reporting group title | Part 1: Safety Run-in |
| Reporting group description: Subjects received Debio 1562 0.7 mg/kg, intravenous (IV) infusion followed by rituximab 375 mg/m ² IV infusion, once on Day 1 of 21-day cycles until the study discontinuation criteria were met (until they develop disease progression, death, unacceptable toxicity, withdraw consent, start new anti-lymphoma treatment or the Sponsor terminates the study). | |
| Reporting group title | Part 1: Cohort 1 |
| Reporting group description: Subjects with R/R DLBCL received Debio 1562 0.7 mg/kg, IV infusion followed by rituximab 375 mg/m ² IV infusion, once on Day 1 of 21-day cycles until the study discontinuation criteria were met (until they develop disease progression, death, unacceptable toxicity, withdraw consent, start new anti-lymphoma treatment or the Sponsor terminates the study). | |
| Reporting group title | Part 1: Cohort 2 |
| Reporting group description: Subjects with R/R NHL received Debio 1562 0.7 mg/kg, IV infusion followed by rituximab 375 mg/m ² IV infusion, once on Day 1 of 21-day cycles until the study discontinuation criteria were met (until they develop disease progression, death, unacceptable toxicity, withdraw consent, start new anti-lymphoma treatment or the Sponsor terminates the study). | |
| Reporting group title | Part 2/3: Cohort A |
| Reporting group description: Subjects with relapsed DLBCL received Debio 1562 0.7 mg/kg, IV infusion followed by rituximab 375 mg/m ² IV infusion, once on Day 1 of a 21-day cycle for at least 6 cycles. | |
| Reporting group title | Part 2/3: Cohort B |
| Reporting group description: Subjects with relapsed DLBCL received Debio 1562 0.4 mg/kg IV infusion followed by rituximab 375 mg/m ² IV infusion on Day 1, then Debio 1562 0.2 mg/kg IV infusion on Days 8 and 15 of a 21-day cycle for at least 6 cycles. | |

| Reporting group values | Part 1: Safety Run-in | Part 1: Cohort 1 | Part 1: Cohort 2 |
|------------------------|-----------------------|------------------|------------------|
| Number of subjects | 17 | 8 | 12 |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|------------------------|---------|--------|--------|
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 68.5 | 70.1 | 68.5 |
| standard deviation | ± 13.05 | ± 9.79 | ± 5.92 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 5 | 5 | 5 |
| Male | 12 | 3 | 7 |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 1 | 1 | 0 |
| Not Hispanic or Latino | 15 | 5 | 12 |
| Not Reported | 1 | 2 | 0 |
| Race | | | |
| Units: Subjects | | | |
| White | 16 | 7 | 11 |

| | | | |
|------------------|---|---|---|
| African American | 0 | 0 | 0 |
| Asian | 1 | 0 | 1 |
| Not Reported | 0 | 1 | 0 |
| Other | 0 | 0 | 0 |

| Reporting group values | Part 2/3: Cohort A | Part 2/3: Cohort B | Total |
|------------------------------------|--------------------|--------------------|-------|
| Number of subjects | 33 | 30 | 100 |
| Age categorical Units: Subjects | | | |

| | | | |
|---|-----------------|-----------------|----|
| Age continuous Units: years arithmetic mean standard deviation | 65.7 ± 13.26 | 68.7 ± 11.78 | - |
| Gender categorical Units: Subjects | | | |
| Female | 14 | 15 | 44 |
| Male | 19 | 15 | 56 |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 1 | 2 | 5 |
| Not Hispanic or Latino | 32 | 28 | 92 |
| Not Reported | 0 | 0 | 3 |
| Race Units: Subjects | | | |
| White | 31 | 30 | 95 |
| African American | 1 | 0 | 1 |
| Asian | 0 | 0 | 2 |
| Not Reported | 0 | 0 | 1 |
| Other | 1 | 0 | 1 |

End points

End points reporting groups

| | |
|---|-----------------------|
| Reporting group title | Part 1: Safety Run-in |
| Reporting group description: Subjects received Debio 1562 0.7 mg/kg, intravenous (IV) infusion followed by rituximab 375 mg/m ² IV infusion, once on Day 1 of 21-day cycles until the study discontinuation criteria were met (until they develop disease progression, death, unacceptable toxicity, withdraw consent, start new anti-lymphoma treatment or the Sponsor terminates the study). | |
| Reporting group title | Part 1: Cohort 1 |
| Reporting group description: Subjects with R/R DLBCL received Debio 1562 0.7 mg/kg, IV infusion followed by rituximab 375 mg/m ² IV infusion, once on Day 1 of 21-day cycles until the study discontinuation criteria were met (until they develop disease progression, death, unacceptable toxicity, withdraw consent, start new anti-lymphoma treatment or the Sponsor terminates the study). | |
| Reporting group title | Part 1: Cohort 2 |
| Reporting group description: Subjects with R/R NHL received Debio 1562 0.7 mg/kg, IV infusion followed by rituximab 375 mg/m ² IV infusion, once on Day 1 of 21-day cycles until the study discontinuation criteria were met (until they develop disease progression, death, unacceptable toxicity, withdraw consent, start new anti-lymphoma treatment or the Sponsor terminates the study). | |
| Reporting group title | Part 2/3: Cohort A |
| Reporting group description: Subjects with relapsed DLBCL received Debio 1562 0.7 mg/kg, IV infusion followed by rituximab 375 mg/m ² IV infusion, once on Day 1 of a 21-day cycle for at least 6 cycles. | |
| Reporting group title | Part 2/3: Cohort B |
| Reporting group description: Subjects with relapsed DLBCL received Debio 1562 0.4 mg/kg IV infusion followed by rituximab 375 mg/m ² IV infusion on Day 1, then Debio 1562 0.2 mg/kg IV infusion on Days 8 and 15 of a 21-day cycle for at least 6 cycles. | |

Primary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs)

| | |
|--|--|
| End point title | Number of Subjects With Treatment-emergent Adverse Events (TEAEs) ^[1] |
| End point description: An AE was defined as any noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic function as indicated by physical signs, symptoms, or laboratory changes occurring in any phase of a clinical study, whether or not considered study drug related. This included exacerbation of a pre-existing condition. AEs included worsening (change in nature, severity, or frequency) of conditions present at the onset of the study, intercurrent illnesses, drug interactions, events related to or possibly related to concomitant medications, abnormal laboratory values (this included significant shifts from baseline within the range of normal that the Investigator considered to be clinically important), clinically significant abnormalities in physical examination, vital signs, and weight. Safety population included all subjects from the screened population who received at least one dose of Debio 1562. | |
| End point type | Primary |
| End point timeframe: Up to 30 days after end of treatment (EOT) (Up to 38 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: Only descriptive statistical analysis was planned to be reported for this endpoint.

| End point values | Part 1: Safety Run-in | Part 1: Cohort 1 | Part 1: Cohort 2 | Part 2/3: Cohort A |
|--------------------------------|-----------------------|------------------|------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 17 | 8 | 12 | 33 |
| Units: subjects with any TEAEs | 16 | 8 | 12 | 32 |

| End point values | Part 2/3: Cohort B | | | |
|--------------------------------|--------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 30 | | | |
| Units: subjects with any TEAEs | 29 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Clinically Significant Changes in Clinical Laboratory Test Results Reported as TEAEs

| | |
|-----------------|---|
| End point title | Number of Subjects With Clinically Significant Changes in Clinical Laboratory Test Results Reported as TEAEs ^[2] |
|-----------------|---|

End point description:

The clinical laboratory tests included Hematology: Hematocrit (Hct),hemoglobin (Hgb),platelet count, red blood cell (RBC) count, white blood cell (WBC) count with differential; Serum Chemistry: Albumin (ALB),alkaline phosphatase(ALK-P),alanine aminotransferase(ALT), serum glutamic pyruvic transaminase; (SGPT), aspartate aminotransferase (AST), serum glutamic oxaloacetic transaminase (SGOT),blood urea nitrogen (BUN),calcium(Ca),chloride(Cl),creatinine, glucose, lactate dehydrogenase(LDH),magnesium, phosphorus, potassium(K),sodium(Na),total bilirubin, total protein, uric acid, immunoglobulin levels(IgG, IgA, IgM); Urinalysis: Appearance, specific gravity and pH, evaluation of glucose, protein, bilirubin, ketones, leukocytes and blood; Coagulation: Prothrombin time(PT) or international normalized ratio(INR),activated partial thromboplastin time(aPTT). Safety population= all subjects from the screened population who received at least one dose of Debio 1562.

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

End point timeframe:

Up to 30 days after EOT (Up to 38 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: Only descriptive statistical analysis was planned to be reported for this endpoint.

| End point values | Part 1: Safety Run-in | Part 1: Cohort 1 | Part 1: Cohort 2 | Part 2/3: Cohort A |
|-----------------------------|-----------------------|------------------|------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 17 | 8 | 12 | 33 |
| Units: subjects | | | | |
| Neutrophil Count Decreased | 6 | 1 | 2 | 2 |
| Lymphocyte Count Decreased | 5 | 1 | 0 | 0 |
| WBC Count Decreased | 5 | 0 | 0 | 1 |
| Platelet Count Decreased | 4 | 1 | 3 | 0 |
| Anaemia | 0 | 2 | 2 | 7 |
| Leukopenia | 0 | 1 | 1 | 5 |
| Neutropenia | 1 | 1 | 4 | 21 |

| | | | | |
|--------------------------------------|---|---|---|---|
| Lymphopenia | 0 | 0 | 0 | 8 |
| Hypophosphataemia | 1 | 0 | 1 | 1 |
| Thrombocytopenia | 0 | 1 | 1 | 4 |
| Febrile Neutropenia | 2 | 0 | 1 | 1 |
| AST Increased | 2 | 2 | 1 | 0 |
| ALK-P Increased | 3 | 0 | 1 | 1 |
| ALT Increased | 2 | 1 | 0 | 1 |
| Blood Creatinine Increased | 0 | 1 | 1 | 1 |
| Hemoglobin Decreased | 2 | 0 | 0 | 0 |
| Blood Immunoglobulin G Decreased | 0 | 0 | 0 | 1 |
| Blood Magnesium Decreased | 0 | 0 | 0 | 0 |
| Hyperkalaemia | 1 | 1 | 2 | 0 |
| Hypoalbuminaemia | 0 | 0 | 0 | 2 |
| Hypercalcaemia | 1 | 0 | 0 | 2 |
| Hyperglycaemia | 0 | 0 | 0 | 2 |
| Hypernatraemia | 0 | 0 | 1 | 0 |
| Hyponatraemia | 2 | 0 | 0 | 0 |
| Hyperphosphataemia | 0 | 0 | 0 | 0 |
| Hyperuricaemia | 0 | 0 | 1 | 1 |
| Hypoglycaemia | 1 | 0 | 1 | 0 |
| Hypomagnesaemia | 0 | 0 | 1 | 1 |
| Blood Bilirubin Increased | 1 | 0 | 0 | 1 |
| Hypokalaemia | 2 | 0 | 2 | 0 |
| Gamma-glutamyl transferase Increased | 0 | 0 | 0 | 2 |

| End point values | Part 2/3: Cohort B | | | |
|----------------------------------|-----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 30 | | | |
| Units: subjects | | | | |
| Neutrophil Count Decreased | 2 | | | |
| Lymphocyte Count Decreased | 0 | | | |
| WBC Count Decreased | 3 | | | |
| Platelet Count Decreased | 2 | | | |
| Anaemia | 6 | | | |
| Leukopenia | 7 | | | |
| Neutropenia | 17 | | | |
| Lymphopenia | 6 | | | |
| Hypophosphataemia | 0 | | | |
| Thrombocytopenia | 6 | | | |
| Febrile Neutropenia | 1 | | | |
| AST Increased | 1 | | | |
| ALK-P Increased | 1 | | | |
| ALT Increased | 1 | | | |
| Blood Creatinine Increased | 0 | | | |
| Hemoglobin Decreased | 0 | | | |
| Blood Immunoglobulin G Decreased | 1 | | | |
| Blood Magnesium Decreased | 0 | | | |
| Hyperkalaemia | 2 | | | |

| | | | | |
|--------------------------------------|---|--|--|--|
| Hypoalbuminaemia | 0 | | | |
| Hypercalcaemia | 1 | | | |
| Hyperglycaemia | 0 | | | |
| Hypernatraemia | 1 | | | |
| Hyponatraemia | 1 | | | |
| Hyperphosphataemia | 0 | | | |
| Hyperuricaemia | 0 | | | |
| Hypoglycaemia | 0 | | | |
| Hypomagnesaemia | 0 | | | |
| Blood Bilirubin Increased | 0 | | | |
| Hypokalaemia | 2 | | | |
| Gamma-glutamyl transferase Increased | 1 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Clinically Significant Changes in Electrocardiogram (ECG) Reported as TEAEs

| | |
|-----------------|--|
| End point title | Number of Subjects With Clinically Significant Changes in Electrocardiogram (ECG) Reported as TEAEs ^[3] |
|-----------------|--|

End point description:

A standard 12-lead ECG was performed. Safety population included all subjects from the screened population who received at least one dose of Debio 1562.

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

End point timeframe:

Up to 30 days after EOT (Up to 38 months)

Notes:

[3] - 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: Only descriptive statistical analysis was planned to be reported for this endpoint.

| End point values | Part 1: Safety Run-in | Part 1: Cohort 1 | Part 1: Cohort 2 | Part 2/3: Cohort A |
|--------------------------------|-----------------------|------------------|------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 17 | 8 | 12 | 33 |
| Units: subjects | | | | |
| Atrial Fibrillation | 0 | 0 | 1 | 0 |
| Electrocardiogram QT prolonged | 0 | 0 | 0 | 1 |
| Acute myocardial infarction | 1 | 0 | 1 | 0 |

| End point values | Part 2/3: Cohort B | | | |
|--------------------------------|--------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 30 | | | |
| Units: subjects | | | | |
| Atrial Fibrillation | 1 | | | |
| Electrocardiogram QT prolonged | 1 | | | |

| | | | | |
|-----------------------------|---|--|--|--|
| Acute myocardial infarction | 0 | | | |
|-----------------------------|---|--|--|--|

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Clinically Significant Changes in Vital Sign Measurements Reported as TEAEs

| | |
|-----------------|--|
| End point title | Number of Subjects With Clinically Significant Changes in Vital Sign Measurements Reported as TEAEs ^[4] |
|-----------------|--|

End point description:

Vital signs included systolic and diastolic blood pressure, heart rate, temperature, and respiratory rate. Safety population included all subjects from the screened population who received at least one dose of Debio 1562.

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

End point timeframe:

Up to 30 days after EOT (Up to 38 months)

Notes:

[4] - 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: Only descriptive statistical analysis was planned to be reported for this endpoint.

| End point values | Part 1: Safety Run-in | Part 1: Cohort 1 | Part 1: Cohort 2 | Part 2/3: Cohort A |
|-----------------------------|-----------------------|------------------|------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 17 | 8 | 12 | 33 |
| Units: subjects | | | | |
| Body Temperature Increased | 1 | 0 | 0 | 1 |
| Hypertension | 0 | 0 | 0 | 3 |
| Hypotension | 0 | 0 | 1 | 1 |
| Pyrexia | 4 | 2 | 1 | 6 |
| Hyperthermia | 0 | 0 | 0 | 0 |
| Tachycardia | 1 | 0 | 0 | 0 |

| End point values | Part 2/3: Cohort B | | | |
|-----------------------------|--------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 30 | | | |
| Units: subjects | | | | |
| Body Temperature Increased | 0 | | | |
| Hypertension | 2 | | | |
| Hypotension | 0 | | | |
| Pyrexia | 4 | | | |
| Hyperthermia | 2 | | | |
| Tachycardia | 1 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Objective Response Rate (ORR)

| | |
|-----------------|--|
| End point title | Objective Response Rate (ORR) ^[5] |
|-----------------|--|

End point description:

ORR was defined as the percentage of subjects with a Best overall response (BOR) of partial response (PR) or complete response (CR). BOR was the best response recorded from the start of the treatment until disease progression, initiation of new anti-cancer therapy, or end of the study period, whichever occurred first. CR was defined as disappearance of all target lesions, no new lesions formation. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to ≤ 1.5 cm. PR was defined as $\geq 50\%$ decrease in the sum of diameters of up to 6 target measurable nodes or extranodal sites, no new lesions formation. Efficacy Evaluable (EE) population included all subjects who received at least one dose of Debio 1562 and rituximab and had both baseline and post-baseline evaluable disease assessments (including clinical progressive disease [PD]).

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

End point timeframe:

Up to PD or death (up to approximately 55 months) or initiation of new anti-cancer therapy whichever occurs first

Notes:

[5] - 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: Statistical analysis data was provided as an attachment due to database constraints.

| End point values | Part 1: Safety Run-in | Part 1: Cohort 1 | Part 1: Cohort 2 | Part 2/3: Cohort A |
|----------------------------------|-----------------------|--------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 15 | 8 | 11 | 30 |
| Units: percent responders | | | | |
| number (confidence interval 95%) | 26.7 (7.8 to 55.1) | 12.5 (0.3 to 52.7) | 81.8 (48.2 to 97.7) | 50.0 (31.3 to 68.7) |

| End point values | Part 2/3: Cohort B | | | |
|----------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 30 | | | |
| Units: percent responders | | | | |
| number (confidence interval 95%) | 50.0 (31.3 to 68.7) | | | |

| | |
|----------------------------|--|
| Attachments (see zip file) | Objective Response Rate -Statistical analysis data/Objective |
|----------------------------|--|

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter: Maximum Plasma Concentration (Cmax) of Debio 1562 and Rituximab

| | |
|--|---|
| End point title | PK Parameter: Maximum Plasma Concentration (Cmax) of Debio 1562 and Rituximab |
| End point description: | |
| PK population included all subjects who received at least one dose of Debio 1562 or rituximab and had atleast one PK concentration result available. Number analysed signifies the number of participants with available data at the specific timepoint. 99999= Data cannot be calculated due to low number of events. | |
| End point type | Secondary |
| End point timeframe: | |
| Parts 1, 2/3: Pre and Post infusion: 5 min-Day (D) 1 of Cycles (C) 1-8 and 2 hours (h)-D1 of C1-2 (for Part 2/3), 24h-D2, 48h-D3 and D8, 15 of C1, 2; D1 of Month 37 (EOT) (rituximab only) and Month 38 (follow-up) (Cycle=21 days) | |

| End point values | Part 1: Safety Run-in | Part 1: Cohort 1 | Part 1: Cohort 2 | Part 2/3: Cohort A |
|--|-----------------------|------------------------|------------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 17 | 8 | 12 | 32 |
| Units: nanogram per milliliter (ng/ml) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Debio 1562: Cycle 1 (n=17,8,12,32,29) | 10005.9 (± 4147.35) | 9411.5 (± 7762.98) | 11821.2 (± 5456.11) | 15339.4 (± 3514.51) |
| Debio 1562: Cycle 2 (n=14,6,7,29,24) | 8697.9 (± 3540.53) | 7775.0 (± 2646.11) | 10521.4 (± 3448.39) | 13868.6 (± 4143.59) |
| Debio 1562: Cycle 3 (n=10,4,9,18,19) | 10600.0 (± 3879.40) | 11472.5 (± 3684.63) | 13682.2 (± 3093.84) | 14324.4 (± 5532.63) |
| Debio 1562: Cycle 4 (n=9,3,9,16,17) | 7787.8 (± 3334.11) | 9230.0 (± 1980.08) | 11703.3 (± 2284.15) | 12560.0 (± 4625.17) |
| Debio 1562: Cycle 5 (n=7,2,8,14,16) | 9744.3 (± 1816.91) | 9675.0 (± 1308.15) | 13220.0 (± 2049.06) | 13487.1 (± 4458.46) |
| Debio 1562: Cycle 6 (n=6,2,8,14,14) | 8050.0 (± 2418.64) | 10195.0 (± 3825.45) | 12983.8 (± 3182.10) | 13025.7 (± 5043.89) |
| Debio 1562: Cycle 7 (n=5,1,7,0,0) | 7908.0 (± 3111.60) | 9940.0 (± 9999) | 12600.0 (± 1803.70) | 99999 (± 99999) |
| Debio 1562: Cycle 8 (n=3,0,8,0,0) | 2253.0 (± 2214.31) | 99999 (± 99999) | 12501.3 (± 2658.79) | 99999 (± 99999) |
| Debio 1562: Month 38(n=0,0,0,0,1) | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) |
| Rituximab: Cycle 1 (n=16,8,12,32,29) | 213287.4 (± 55735.54) | 207415.8 (± 67408.74) | 179430.7 (± 41213.48) | 170942.3 (± 28871.50) |
| Rituximab: Cycle 2 (n=14,7,11,29,24) | 251697.6 (± 41113.07) | 214761.9 (± 40919.84) | 191988.5 (± 65788.33) | 205481.9 (± 43738.73) |
| Rituximab: Cycle 3 (n=9,4,9,18,18) | 272302.8 (± 58497.66) | 213378.8 (± 36470.96) | 239380.8 (± 60127.34) | 218358.1 (± 49891.16) |
| Rituximab: Cycle 4 (n=8,3,9,16,17) | 283067.9 (± 57414.89) | 198313.3 (± 79455.19) | 262263.9 (± 67895.19) | 236146.8 (± 63699.49) |
| Rituximab: Cycle 5 (n=7,2,8,14,15) | 366032.9 (± 94593.53) | 156582.0 (± 82703.21) | 266406.1 (± 52480.70) | 282017.6 (± 66512.79) |
| Rituximab: Cycle 6 (n=6,2,8,14,14) | 354142.7 (± 90095.73) | 200913.0 (± 130086.43) | 240735.0 (± 114120.93) | 294989.5 (± 82301.31) |
| Rituximab: Cycle 7 (n=5,1,7,1,0) | 341761.4 (± 37261.58) | 179381.0 (± 99999) | 281045.9 (± 62528.32) | 114902.0 (± 99999) |

| | | | | |
|-------------------------------------|-----------------------|----------------------|-----------------------|----------------------|
| Rituximab: Cycle 8 (n=3,0,8,0,0) | 379038.7 (± 83552.42) | 99999 (± 99999) | 251326.4 (± 85797.08) | 99999 (± 99999) |
| Rituximab: Month 37 (n=9,4,8,13,14) | 77330.7 (± 34343.07) | 59503.5 (± 9683.76) | 53960.9 (± 61954.05) | 86046.4 (± 53904.82) |
| Rituximab: Month 38(n=12,5,7,20,20) | 107690.6 (± 56044.52) | 82585.0 (± 31312.62) | 78777.3 (± 72013.43) | 69646.9 (± 49779.31) |

| End point values | Part 2/3: Cohort B | | | |
|--|------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 29 | | | |
| Units: nanogram per milliliter (ng/ml) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Debio 1562: Cycle 1 (n=17,8,12,32,29) | 6612.4 (± 2315.16) | | | |
| Debio 1562: Cycle 2 (n=14,6,7,29,24) | 8465.5 (± 6553.50) | | | |
| Debio 1562: Cycle 3 (n=10,4,9,18,19) | 6824.0 (± 2911.62) | | | |
| Debio 1562: Cycle 4 (n=9,3,9,16,17) | 7122.9 (± 3084.39) | | | |
| Debio 1562: Cycle 5 (n=7,2,8,14,16) | 7305.0 (± 3089.01) | | | |
| Debio 1562: Cycle 6 (n=6,2,8,14,14) | 6904.3 (± 2516.11) | | | |
| Debio 1562: Cycle 7 (n=5,1,7,0,0) | 99999 (± 99999) | | | |
| Debio 1562: Cycle 8 (n=3,0,8,0,0) | 99999 (± 99999) | | | |
| Debio 1562: Month 38(n=0,0,0,0,1) | 15000.0 (± 99999) | | | |
| Rituximab: Cycle 1 (n=16,8,12,32,29) | 171006.4 (± 37226.83) | | | |
| Rituximab: Cycle 2 (n=14,7,11,29,24) | 210563.7 (± 43723.39) | | | |
| Rituximab: Cycle 3 (n=9,4,9,18,18) | 254760.9 (± 107449.36) | | | |
| Rituximab: Cycle 4 (n=8,3,9,16,17) | 267141.2 (± 65390.99) | | | |
| Rituximab: Cycle 5 (n=7,2,8,14,15) | 267163.1 (± 51180.64) | | | |
| Rituximab: Cycle 6 (n=6,2,8,14,14) | 296240.1 (± 68962.34) | | | |
| Rituximab: Cycle 7 (n=5,1,7,1,0) | 99999 (± 99999) | | | |
| Rituximab: Cycle 8 (n=3,0,8,0,0) | 99999 (± 99999) | | | |
| Rituximab: Month 37 (n=9,4,8,13,14) | 73469.1 (± 47009.66) | | | |
| Rituximab: Month 38(n=12,5,7,20,20) | 79561.6 (± 55656.86) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

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

End point description:

PFS was defined as the duration between the first dose date of Debio 1562 and the date of progressive disease (PD) or death due to any cause, whichever occurs first. PD is defined as the new or clear progression of preexisting non-measured lesions or regrowth of previously resolved lesions or a new node >1.5 cm in any axis or an abnormal lesion with >1.5 cm longest transverse diameter or increase by >50% of lesion. EE population included all subjects who received at least one dose of Debio 1562 and rituximab and had both baseline and post-baseline evaluable disease assessments (including clinical PD). 99999=Data is not available due to low number of events.

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

End point timeframe:

Up to PD or death or end of study (approximately 57 months) or initiation of new anti-cancer therapy whichever occurs first

| End point values | Part 1: Safety Run-in | Part 1: Cohort 1 | Part 1: Cohort 2 | Part 2/3: Cohort A |
|----------------------------------|-----------------------|------------------|----------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 15 | 8 | 11 | 30 |
| Units: months | | | | |
| median (confidence interval 95%) | 1.4 (1.2 to 11.1) | 1.8 (1.3 to 4.0) | 20.7 (10.5 to 99999) | 5.1 (1.4 to 99999) |

| End point values | Part 2/3: Cohort B | | | |
|----------------------------------|--------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 30 | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 4.6 (1.4 to 13.4) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response (TTR)

| | |
|-----------------|------------------------|
| End point title | Time to Response (TTR) |
|-----------------|------------------------|

End point description:

TTR was defined as the duration between the first dose date of Debio 1562 and the date of first objective response (PR or CR). CR was defined as disappearance of all target lesions, no new lesions formation. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to ≤ 1.5 cm. PR was defined as $\geq 50\%$ decrease in the sum of diameters of up to 6 target measurable nodes or extranodal sites, no new lesions formation. EE population included all subjects who received at least one dose of Debio 1562 and rituximab and had both baseline and post-baseline evaluable disease assessments (including clinical PD). Data is reported only for participants who responded. 99999= Data is not available due to low number of subjects with events.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to PD or death or end of study (approximately 57 months) or initiation of new anti-cancer therapy whichever occurs first | |

| End point values | Part 1: Safety Run-in | Part 1: Cohort 1 | Part 1: Cohort 2 | Part 2/3: Cohort A |
|----------------------------------|-----------------------|--------------------|------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4 | 1 | 9 | 15 |
| Units: months | | | | |
| median (confidence interval 95%) | 1.4 (1.2 to 99999) | 1.4 (0.0 to 99999) | 1.4 (1.4 to 2.1) | 1.5 (1.4 to 1.8) |

| End point values | Part 2/3: Cohort B | | | |
|----------------------------------|--------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 15 | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 1.5 (1.4 to 3.3) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

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

End point description:

DoR was defined as duration between date of the first objective response (PR or CR) and date of PD or death due to any cause, whichever occurs first. CR: Disappearance of all target lesions, no new lesions formation, any pathological lymph nodes (whether target or non-target) must have reduction in short axis to ≤ 1.5 cm. PR: $\geq 50\%$ decrease in sum of diameters of up to 6 target measurable nodes or extranodal sites, no new lesions formation. PD: New or clear progression of preexisting non-measured lesions or regrowth of previously resolved lesions or a new node >1.5 cm in any axis or an abnormal lesion with >1.5 cm longest transverse diameter or increase by $>50\%$ of lesion. EE population included all subjects who received at least one dose of Debio 1562 and rituximab and had both baseline and post-baseline evaluable disease assessments (including clinical PD). Data is reported only for subjects who responded. 99999=Data is not available due to low number of events.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to PD or death or end of study (approximately 57 months) or initiation of new anti-cancer therapy whichever occurs first | |

| End point values | Part 1: Safety Run-in | Part 1: Cohort 1 | Part 1: Cohort 2 | Part 2/3: Cohort A |
|----------------------------------|-----------------------|--------------------|-----------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4 | 1 | 9 | 15 |
| Units: months | | | | |
| median (confidence interval 95%) | 99999 (9.7 to 99999) | 2.6 (0.0 to 99999) | 99999 (13.2 to 99999) | 99999 (13.6 to 99999) |

| End point values | Part 2/3: Cohort B | | | |
|----------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 15 | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 16.5 (3.4 to 99999) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

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

End point description:

OS was defined as the duration between the first dose date of Debio 1562 and the date of death due to any cause. EE population included all subjects who received at least one dose of Debio 1562 and rituximab and had both baseline and post-baseline evaluable disease assessments (including clinical PD). 99999= Data is not available due to low number of subjects with events.

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

End point timeframe:

Up to death or end of study (approximately 57 months) or one year from the last participant`s first dose

| End point values | Part 1: Safety Run-in | Part 1: Cohort 1 | Part 1: Cohort 2 | Part 2/3: Cohort A |
|----------------------------------|-----------------------|-------------------|----------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 15 | 8 | 11 | 30 |
| Units: months | | | | |
| median (confidence interval 95%) | 30.0 (13.3 to 99999) | 8.4 (2.7 to 17.0) | 34.3 (24.3 to 99999) | 99999 (11.4 to 99999) |

| End point values | Part 2/3: Cohort B | | | |
|-----------------------------|--------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 30 | | | |
| Units: months | | | | |

| | | | | |
|----------------------------------|---------------------|--|--|--|
| median (confidence interval 95%) | 17.3 (9.5 to 99999) | | | |
|----------------------------------|---------------------|--|--|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Anti-drug Antibodies (ADA) for Debio 1562

| | |
|-----------------|---|
| End point title | Number of Subjects With Anti-drug Antibodies (ADA) for Debio 1562 |
|-----------------|---|

End point description:

The potential immunogenicity against Debio 1562 was assessed in an ADA population, which included all subjects who received at least one dose of Debio 1562 or rituximab and had at least one ADA post exposure result available. Number analysed signifies number of subjects with non-missing ADA value at baseline and at least one non-missing post-treatment value.

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

End point timeframe:

Part 1: Pre-dose on Day 1 of Cycle(C)1 to 8; Part 2/3: Pre-dose on Day 1 of C1 to 6 and on Day 1 of C7 for participants who received treatment beyond C6 (each C=21 days); Parts 1, 2/3: Month 37 (EOT) and Month 38 (30-Day FU visit) (Cycle=21 days)

| End point values | Part 1: Safety Run-in | Part 1: Cohort 1 | Part 1: Cohort 2 | Part 2/3: Cohort A |
|-------------------------------------|-----------------------|------------------|------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 14 | 6 | 10 | 30 |
| Units: subjects | | | | |
| No Change From Baseline | 13 | 6 | 10 | 25 |
| Decrease in ADA Titer From Baseline | 1 | 0 | 0 | 3 |
| Increase in ADA Titer From Baseline | 0 | 0 | 0 | 2 |

| End point values | Part 2/3: Cohort B | | | |
|-------------------------------------|--------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 25 | | | |
| Units: subjects | | | | |
| No Change From Baseline | 20 | | | |
| Decrease in ADA Titer From Baseline | 3 | | | |
| Increase in ADA Titer From Baseline | 2 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality: Up to end of study (approximately 57 months); Adverse events: Up to 30 days after EOT (Up to 38 months)

Adverse event reporting additional description:

Safety Population included all subjects from the screened population who received at least 1 dose of Debio 1562.

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

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 23.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------------------|
| Reporting group title | Part 1: Safety Run-in |
|-----------------------|-----------------------|

Reporting group description:

Subjects received Debio 1562 0.7 mg/kg, IV infusion followed by rituximab 375 mg/m² IV infusion, once on Day 1 of 21-day cycles until the study discontinuation criteria were met (until they develop disease progression, death, unacceptable toxicity, withdraw consent, start new anti-lymphoma treatment or the Sponsor terminates the study).

| | |
|-----------------------|------------------|
| Reporting group title | Part 1: Cohort 1 |
|-----------------------|------------------|

Reporting group description:

Subjects with R/R DLBCL received Debio 1562 0.7 mg/kg, IV infusion followed by rituximab 375 mg/m² IV infusion, once on Day 1 of 21-day cycles until the study discontinuation criteria were met (until they develop disease progression, death, unacceptable toxicity, withdraw consent, start new anti-lymphoma treatment or the Sponsor terminates the study).

| | |
|-----------------------|------------------|
| Reporting group title | Part 1: Cohort 2 |
|-----------------------|------------------|

Reporting group description:

Subjects with R/R NHL received Debio 1562 0.7 mg/kg, IV infusion followed by rituximab 375 mg/m² IV infusion, once on Day 1 of 21-day cycles until the study discontinuation criteria were met (until they develop disease progression, death, unacceptable toxicity, withdraw consent, start new anti-lymphoma treatment or the Sponsor terminates the study).

| | |
|-----------------------|--------------------|
| Reporting group title | Part 2/3: Cohort A |
|-----------------------|--------------------|

Reporting group description:

Subjects with relapsed DLBCL received Debio 1562 0.7 mg/kg, IV infusion followed by rituximab 375 mg/m² IV infusion, once on Day 1 of a 21-day cycle for at least 6 cycles.

| | |
|-----------------------|--------------------|
| Reporting group title | Part 2/3: Cohort B |
|-----------------------|--------------------|

Reporting group description:

Subjects with relapsed DLBCL received Debio 1562 0.4 mg/kg IV infusion followed by rituximab 375 mg/m² IV infusion on Day 1, then Debio 1562 0.2 mg/kg IV infusion on Days 8 and 15 of a 21-day cycle for at least 6 cycles.

| Serious adverse events | Part 1: Safety Run-in | Part 1: Cohort 1 | Part 1: Cohort 2 |
|---|-----------------------|------------------|------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 17 (29.41%) | 3 / 8 (37.50%) | 5 / 12 (41.67%) |
| number of deaths (all causes) | 11 | 6 | 5 |
| number of deaths resulting from adverse events | 1 | 0 | 2 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |

| | | | |
|--|----------------|----------------|----------------|
| Adenocarcinoma of colon | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Intraductal papillary mucinous neoplasm | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour pain | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 8 (12.50%) | 0 / 12 (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 |
| Vascular disorders | | | |
| Aortic stenosis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Circulatory collapse | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple organ dysfunction syndrome | | | |

| | | | |
|---|----------------|---------------|----------------|
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Prostatitis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinus pain | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (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 |
| Injury, poisoning and procedural complications | | | |
| Humerus fracture | | | |

| | | | |
|---|----------------|---------------|----------------|
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (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 |
| Infusion related reaction | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural fever | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure chronic | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Left ventricular failure | | | |

| | | | |
|---|-----------------|---------------|----------------|
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (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 |
| Hypoglycaemic seizure | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anaemia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oral pain | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (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 |

| | | | |
|---|----------------|----------------|----------------|
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Hepatitis toxic | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Haematuria | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 8 (12.50%) | 0 / 12 (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 |
| Chondrocalcinosis pyrophosphate | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Soft tissue mass | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 8 (12.50%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| COVID-19 | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 8 (12.50%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 8 (12.50%) | 0 / 12 (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 |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (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 |
| Device related infection | | | |

| | | | |
|---|----------------|---------------|----------------|
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gangrene | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinusitis aspergillus | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (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 |

| Serious adverse events | Part 2/3: Cohort A | Part 2/3: Cohort B | |
|---|--------------------|--------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 15 / 33 (45.45%) | 9 / 30 (30.00%) | |
| number of deaths (all causes) | 16 | 17 | |
| number of deaths resulting from adverse events | 5 | 2 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adenocarcinoma of colon | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intraductal papillary mucinous neoplasm | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour pain | | | |

| | | | |
|--|----------------|----------------|--|
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Aortic stenosis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Circulatory collapse | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 30 (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 | | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 3 / 33 (9.09%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Reproductive system and breast disorders | | | |
| Prostatitis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 30 (3.33%) | |
| 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 | 0 / 33 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Sinus pain | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infusion related reaction | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural fever | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |

| | | | |
|---|----------------|----------------|--|
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiac failure chronic | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Left ventricular failure | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemic seizure | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oral pain | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Hepatitis toxic | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chondrocalcinosis pyrophosphate | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Soft tissue mass | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 2 / 30 (6.67%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| COVID-19 | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gangrene | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinusitis aspergillus | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |

| | | | |
|---|----------------|----------------|--|
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Part 1: Safety Run-in | Part 1: Cohort 1 | Part 1: Cohort 2 |
|---|-----------------------|------------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 15 / 17 (88.24%) | 8 / 8 (100.00%) | 12 / 12 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant muscle neoplasm | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Seborrhoeic keratosis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Tumour pain | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Flushing | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 2 / 12 (16.67%) |
| occurrences (all) | 0 | 0 | 2 |
| Hot flush | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 8 (12.50%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Lymphostasis | | | |

| | | | |
|--|-----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cyanosis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Phlebitis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 8 / 17 (47.06%) | 1 / 8 (12.50%) | 4 / 12 (33.33%) |
| occurrences (all) | 8 | 1 | 10 |
| Pyrexia | | | |
| subjects affected / exposed | 4 / 17 (23.53%) | 2 / 8 (25.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 5 | 3 | 1 |
| Asthenia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 8 (12.50%) | 4 / 12 (33.33%) |
| occurrences (all) | 2 | 2 | 4 |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 4 / 12 (33.33%) |
| occurrences (all) | 0 | 0 | 10 |
| Chills | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 2 / 12 (16.67%) |
| occurrences (all) | 1 | 0 | 2 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Hyperthermia | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pain | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Facial pain | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Swelling | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Reproductive system and breast disorders | | | |
| Breast pain | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 6 / 17 (35.29%) | 2 / 8 (25.00%) | 6 / 12 (50.00%) |
| occurrences (all) | 12 | 3 | 11 |
| Dyspnoea | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 1 / 8 (12.50%) | 5 / 12 (41.67%) |
| occurrences (all) | 6 | 1 | 10 |
| Nasal congestion | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 2 / 12 (16.67%) |
| occurrences (all) | 1 | 0 | 2 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rhinorrhoea | | | |

| | | | |
|----------------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pharyngeal erythema | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Productive cough | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pulmonary mass | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Stridor | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 0 / 8 (0.00%) | 2 / 12 (16.67%) |
| occurrences (all) | 4 | 0 | 7 |
| Anxiety | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 2 / 12 (16.67%) |
| occurrences (all) | 1 | 0 | 2 |
| Confusional state | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Investigations | | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 6 / 17 (35.29%) | 1 / 8 (12.50%) | 2 / 12 (16.67%) |
| occurrences (all) | 18 | 1 | 4 |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 5 / 17 (29.41%) | 1 / 8 (12.50%) | 0 / 12 (0.00%) |
| occurrences (all) | 23 | 1 | 0 |
| White blood cell count decreased | | | |

| | | | |
|---------------------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed | 5 / 17 (29.41%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 18 | 0 | 0 |
| Platelet count decreased | | | |
| subjects affected / exposed | 4 / 17 (23.53%) | 1 / 8 (12.50%) | 3 / 12 (25.00%) |
| occurrences (all) | 6 | 1 | 7 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 1 / 8 (12.50%) | 0 / 12 (0.00%) |
| occurrences (all) | 4 | 2 | 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 2 / 8 (25.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 2 | 3 | 1 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 3 | 0 | 1 |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 8 (12.50%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Body temperature increased | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Blood lactate dehydrogenase increased | | | |

| | | | |
|--|----------------|---------------|-----------------|
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Cardiac murmur | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Troponin increased | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Weight increased | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| White blood cell count increased | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Infusion related reaction | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Fall | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 2 / 12 (16.67%) |
| occurrences (all) | 0 | 0 | 2 |
| Contusion | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Procedural pain | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 2 |
| Radius fracture | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin abrasion | | | |

| | | | |
|--|---------------------|--------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 8 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Cardiac disorders | | | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 1 / 8 (12.50%) | 4 / 12 (33.33%) |
| occurrences (all) | 2 | 1 | 5 |
| Dizziness | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 8 (12.50%) | 3 / 12 (25.00%) |
| occurrences (all) | 1 | 1 | 3 |
| Dysgeusia | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 2 | 0 | 1 |
| Tremor | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Paraesthesia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Peripheral sensory neuropathy | | | |

| | | | |
|--------------------------------------|----------------|---------------|----------------|
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Akathisia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Cognitive disorder | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Diabetic neuropathy | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 2 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Peripheral motor neuropathy | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Polyneuropathy | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Sciatica | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Taste disorder | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Visual field defect | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood and lymphatic system disorders | | | |

| | | | |
|-------------------------------|-----------------|----------------|-----------------|
| Neutropenia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 8 (12.50%) | 4 / 12 (33.33%) |
| occurrences (all) | 1 | 7 | 15 |
| Lymphopenia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 8 (12.50%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 7 | 4 |
| Anaemia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 8 (25.00%) | 2 / 12 (16.67%) |
| occurrences (all) | 0 | 3 | 5 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 8 (12.50%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Autoimmune haemolytic anaemia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 2 |
| Ear and labyrinth disorders | | | |
| Ear discomfort | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Eye disorders | | | |
| Eye disorder | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Eye pruritus | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 2 / 8 (25.00%) | 5 / 12 (41.67%) |
| occurrences (all) | 5 | 4 | 8 |
| Nausea | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 8 (0.00%) | 4 / 12 (33.33%) |
| occurrences (all) | 3 | 0 | 4 |
| Vomiting | | | |

| | | | |
|----------------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed | 4 / 17 (23.53%) | 0 / 8 (0.00%) | 3 / 12 (25.00%) |
| occurrences (all) | 4 | 0 | 4 |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 8 (12.50%) | 2 / 12 (16.67%) |
| occurrences (all) | 1 | 1 | 3 |
| Constipation | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 1 / 8 (12.50%) | 1 / 12 (8.33%) |
| occurrences (all) | 2 | 2 | 1 |
| Dyspepsia | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 2 | 0 | 4 |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 8 (12.50%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 8 (12.50%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Flatulence | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Proctalgia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Toothache | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dysphagia | | | |

| | | | |
|--|----------------------|---------------------|----------------------|
| subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 8 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Hepatobiliary disorders Hepatocellular injury subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 0 / 8 (0.00%) 0 | 1 / 12 (8.33%) 1 |
| Skin and subcutaneous tissue disorders Night sweats subjects affected / exposed occurrences (all) | 2 / 17 (11.76%) 2 | 1 / 8 (12.50%) 1 | 3 / 12 (25.00%) 3 |
| Pruritus subjects affected / exposed occurrences (all) | 2 / 17 (11.76%) 2 | 0 / 8 (0.00%) 0 | 1 / 12 (8.33%) 2 |
| Rash maculo-papular subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 0 / 8 (0.00%) 0 | 2 / 12 (16.67%) 7 |
| Rash subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 1 / 8 (12.50%) 1 | 2 / 12 (16.67%) 2 |
| Dry skin subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 8 (0.00%) 0 | 1 / 12 (8.33%) 1 |
| Erythema subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 8 (12.50%) 2 | 0 / 12 (0.00%) 0 |
| Exfoliative rash subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 0 / 8 (0.00%) 0 | 1 / 12 (8.33%) 1 |
| Hyperhidrosis subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 8 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Hyperkeratosis subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 0 / 8 (0.00%) 0 | 1 / 12 (8.33%) 1 |
| Lividity | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 8 (12.50%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Onychomadesis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rash pruritic | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin lesion | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin mass | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Renal and urinary disorders | | | |
| Pollakiuria | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Urinary incontinence | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 8 (0.00%) | 3 / 12 (25.00%) |
| occurrences (all) | 2 | 0 | 5 |
| Bone pain | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 0 / 8 (0.00%) | 2 / 12 (16.67%) |
| occurrences (all) | 6 | 0 | 2 |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 3 / 12 (25.00%) |
| occurrences (all) | 1 | 0 | 5 |
| Muscle spasms | | | |

| | | | |
|-----------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 2 / 12 (16.67%) |
| occurrences (all) | 1 | 0 | 2 |
| Myalgia | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 3 | 0 | 1 |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 2 / 12 (16.67%) |
| occurrences (all) | 0 | 0 | 2 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 2 / 12 (16.67%) |
| occurrences (all) | 0 | 0 | 2 |
| Flank pain | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 2 / 12 (16.67%) |
| occurrences (all) | 0 | 0 | 2 |
| Neck pain | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Amyotrophy | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 8 (12.50%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Iliolumbar syndrome | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 8 (12.50%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Joint swelling | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Back pain | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 8 (12.50%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Infections and infestations | | | |

| | | | |
|-----------------------------------|-----------------|----------------|-----------------|
| Urinary tract infection | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 1 / 8 (12.50%) | 0 / 12 (0.00%) |
| occurrences (all) | 4 | 1 | 0 |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 2 / 12 (16.67%) |
| occurrences (all) | 1 | 0 | 2 |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 2 / 12 (16.67%) |
| occurrences (all) | 1 | 0 | 2 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 2 |
| Oral candidiasis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rhinitis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 8 (12.50%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Conjunctivitis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Furuncle | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Laryngitis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Sinusitis aspergillus | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|------------------------------------|-----------------|----------------|-----------------|
| Skin infection | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Tooth abscess | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Tracheobronchitis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Influenza | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 5 / 17 (29.41%) | 1 / 8 (12.50%) | 1 / 12 (8.33%) |
| occurrences (all) | 5 | 1 | 1 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 8 (12.50%) | 2 / 12 (16.67%) |
| occurrences (all) | 1 | 3 | 4 |
| Hypokalaemia | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 8 (0.00%) | 2 / 12 (16.67%) |
| occurrences (all) | 3 | 0 | 2 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Dehydration | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 8 (12.50%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Hyperuricaemia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 2 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Hypernatraemia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 8 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Iron deficiency | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 8 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| Non-serious adverse events | Part 2/3: Cohort A | Part 2/3: Cohort B | |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 32 / 33 (96.97%) | 29 / 30 (96.67%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant muscle neoplasm | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Seborrhoeic keratosis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Tumour pain | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 3 / 33 (9.09%) | 2 / 30 (6.67%) | |
| occurrences (all) | 6 | 4 | |
| Flushing | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hot flush | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Lymphostasis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 30 (6.67%) | |
| occurrences (all) | 0 | 2 | |
| Cyanosis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Phlebitis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 7 / 33 (21.21%) | 2 / 30 (6.67%) | |
| occurrences (all) | 13 | 3 | |
| Pyrexia | | | |
| subjects affected / exposed | 6 / 33 (18.18%) | 4 / 30 (13.33%) | |
| occurrences (all) | 9 | 4 | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 5 / 30 (16.67%) | |
| occurrences (all) | 0 | 6 | |
| Oedema peripheral | | | |

| | | | |
|---|----------------|-----------------|--|
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 30 (6.67%) | |
| occurrences (all) | 0 | 2 | |
| Chills | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 2 / 30 (6.67%) | |
| occurrences (all) | 1 | 2 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 1 / 30 (3.33%) | |
| occurrences (all) | 1 | 1 | |
| Hyperthermia | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 30 (6.67%) | |
| occurrences (all) | 0 | 4 | |
| Pain | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Facial pain | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Swelling | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Reproductive system and breast disorders | | | |
| Breast pain | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 3 / 33 (9.09%) | 2 / 30 (6.67%) | |
| occurrences (all) | 3 | 6 | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 4 / 30 (13.33%) | |
| occurrences (all) | 4 | 4 | |
| Nasal congestion | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Pharyngeal erythema | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Productive cough | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Pulmonary mass | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Stridor | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 2 / 30 (6.67%) | |
| occurrences (all) | 4 | 4 | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Confusional state | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |

| | | | |
|--------------------------------------|----------------|-----------------|--|
| Investigations | | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 2 / 30 (6.67%) | |
| occurrences (all) | 3 | 5 | |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 3 / 30 (10.00%) | |
| occurrences (all) | 1 | 3 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 30 (6.67%) | |
| occurrences (all) | 0 | 4 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 1 / 30 (3.33%) | |
| occurrences (all) | 1 | 1 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 1 / 30 (3.33%) | |
| occurrences (all) | 1 | 1 | |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 1 / 30 (3.33%) | |
| occurrences (all) | 1 | 2 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 1 / 30 (3.33%) | |
| occurrences (all) | 1 | 1 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 1 / 30 (3.33%) | |
| occurrences (all) | 2 | 1 | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Body temperature increased | | | |

| | | | |
|--|----------------|----------------|--|
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Cardiac murmur | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Troponin increased | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Weight increased | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| White blood cell count increased | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Infusion related reaction | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 2 / 30 (6.67%) | |
| occurrences (all) | 3 | 2 | |
| Fall | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Contusion | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Procedural pain | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Radius fracture | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Skin abrasion | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Cardiac disorders | | | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 0 / 30 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 1 / 30 (3.33%) | |
| occurrences (all) | 1 | 3 | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Dysgeusia | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tremor | | | |

| | | |
|-------------------------------|----------------|----------------|
| subjects affected / exposed | 1 / 33 (3.03%) | 2 / 30 (6.67%) |
| occurrences (all) | 1 | 2 |
| Paraesthesia | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 30 (0.00%) |
| occurrences (all) | 1 | 0 |
| Peripheral sensory neuropathy | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 1 / 30 (3.33%) |
| occurrences (all) | 1 | 1 |
| Neuropathy peripheral | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 30 (0.00%) |
| occurrences (all) | 1 | 0 |
| Akathisia | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 0 |
| Cognitive disorder | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 0 |
| Diabetic neuropathy | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 0 |
| Haemorrhage intracranial | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 0 |
| Hypoaesthesia | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 0 |
| Peripheral motor neuropathy | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 0 |
| Polyneuropathy | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 0 |
| Sciatica | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 0 |
| Taste disorder | | |

| | | | |
|---|------------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 33 (0.00%) 0 | 0 / 30 (0.00%) 0 | |
| Visual field defect subjects affected / exposed occurrences (all) | 0 / 33 (0.00%) 0 | 0 / 30 (0.00%) 0 | |
| Blood and lymphatic system disorders | | | |
| Neutropenia subjects affected / exposed occurrences (all) | 21 / 33 (63.64%) 48 | 17 / 30 (56.67%) 52 | |
| Lymphopenia subjects affected / exposed occurrences (all) | 8 / 33 (24.24%) 16 | 6 / 30 (20.00%) 32 | |
| Leukopenia subjects affected / exposed occurrences (all) | 5 / 33 (15.15%) 9 | 7 / 30 (23.33%) 23 | |
| Anaemia subjects affected / exposed occurrences (all) | 7 / 33 (21.21%) 10 | 5 / 30 (16.67%) 7 | |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 4 / 33 (12.12%) 5 | 6 / 30 (20.00%) 9 | |
| Autoimmune haemolytic anaemia subjects affected / exposed occurrences (all) | 0 / 33 (0.00%) 0 | 0 / 30 (0.00%) 0 | |
| Ear and labyrinth disorders | | | |
| Ear discomfort subjects affected / exposed occurrences (all) | 0 / 33 (0.00%) 0 | 0 / 30 (0.00%) 0 | |
| Eye disorders | | | |
| Eye disorder subjects affected / exposed occurrences (all) | 0 / 33 (0.00%) 0 | 0 / 30 (0.00%) 0 | |
| Eye pruritus subjects affected / exposed occurrences (all) | 0 / 33 (0.00%) 0 | 0 / 30 (0.00%) 0 | |
| Gastrointestinal disorders | | | |

| | | |
|----------------------------------|-----------------|-----------------|
| Diarrhoea | | |
| subjects affected / exposed | 5 / 33 (15.15%) | 2 / 30 (6.67%) |
| occurrences (all) | 5 | 3 |
| Nausea | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 4 / 30 (13.33%) |
| occurrences (all) | 2 | 6 |
| Vomiting | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 3 / 30 (10.00%) |
| occurrences (all) | 1 | 3 |
| Abdominal pain | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 6 / 30 (20.00%) |
| occurrences (all) | 0 | 6 |
| Constipation | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 2 / 30 (6.67%) |
| occurrences (all) | 2 | 3 |
| Dyspepsia | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 0 |
| Haemorrhoids | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 1 / 30 (3.33%) |
| occurrences (all) | 2 | 1 |
| Abdominal pain upper | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 3 / 30 (10.00%) |
| occurrences (all) | 1 | 3 |
| Abdominal pain lower | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 30 (3.33%) |
| occurrences (all) | 0 | 2 |
| Flatulence | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 30 (3.33%) |
| occurrences (all) | 0 | 1 |
| Gastrooesophageal reflux disease | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 0 |
| Proctalgia | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 30 (0.00%) |
| occurrences (all) | 2 | 0 |

| | | | |
|--|----------------|----------------|--|
| Stomatitis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Toothache | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hepatobiliary disorders | | | |
| Hepatocellular injury | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Night sweats | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 0 / 30 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Pruritus | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 1 / 30 (3.33%) | |
| occurrences (all) | 3 | 1 | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Rash | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Dry skin | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Erythema | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Exfoliative rash | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hyperhidrosis | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hyperkeratosis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Lividity | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Onychomadesis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Rash pruritic | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Skin lesion | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Skin mass | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Renal and urinary disorders | | | |
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Urinary incontinence | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 3 / 33 (9.09%) | 1 / 30 (3.33%) | |
| occurrences (all) | 4 | 8 | |
| Bone pain | | | |

| | | |
|-----------------------------|----------------|----------------|
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 0 |
| Muscular weakness | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 0 |
| Muscle spasms | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 0 / 30 (0.00%) |
| occurrences (all) | 2 | 0 |
| Myalgia | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 30 (0.00%) |
| occurrences (all) | 1 | 0 |
| Osteoarthritis | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 30 (0.00%) |
| occurrences (all) | 3 | 0 |
| Pain in extremity | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 30 (0.00%) |
| occurrences (all) | 1 | 0 |
| Flank pain | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 30 (0.00%) |
| occurrences (all) | 1 | 0 |
| Musculoskeletal chest pain | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 0 |
| Neck pain | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 30 (3.33%) |
| occurrences (all) | 0 | 1 |
| Amyotrophy | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 0 |
| Iliolumbar syndrome | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 0 |
| Joint swelling | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 0 |
| Musculoskeletal pain | | |

| | | | |
|-----------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Back pain | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 2 / 30 (6.67%) | |
| occurrences (all) | 1 | 3 | |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 3 / 33 (9.09%) | 1 / 30 (3.33%) | |
| occurrences (all) | 5 | 1 | |
| Bronchitis | | | |
| subjects affected / exposed | 4 / 33 (12.12%) | 1 / 30 (3.33%) | |
| occurrences (all) | 5 | 1 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 3 / 30 (10.00%) | |
| occurrences (all) | 0 | 6 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 1 / 30 (3.33%) | |
| occurrences (all) | 2 | 1 | |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 30 (6.67%) | |
| occurrences (all) | 0 | 2 | |
| Oral candidiasis | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Furuncle | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |

| | | | |
|------------------------------------|----------------|-----------------|--|
| Laryngitis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Sinusitis aspergillus | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Skin infection | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Tooth abscess | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Tracheobronchitis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Influenza | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 3 / 30 (10.00%) | |
| occurrences (all) | 1 | 6 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 30 (6.67%) | |
| occurrences (all) | 0 | 3 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 1 / 30 (3.33%) | |
| occurrences (all) | 4 | 2 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 30 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Hypoalbuminaemia | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 2 / 33 (6.06%) | 2 / 30 (6.67%) | |
| occurrences (all) | 2 | 3 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 3 | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hyperuricaemia | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hypernatraemia | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Iron deficiency | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 29 February 2016 | <p>a) Revisions and editing for consistency and clarity</p> <p>b) The exploratory objectives were expanded to include gene expression profiling and genomic analysis of relevant genes, and the corresponding endpoint was revised accordingly</p> <p>c) Inclusion and exclusion criteria and schedule of events were revised</p> <p>d) Toxicity management guidelines were revised to improve consistency and define dose-modifying events</p> <p>e) The guidelines for subject discontinuation and collection of subsequent anti-cancer therapy were revised</p> <p>f) The hematology and serum chemistry assessments and description of record retention were streamlined</p> <p>g) The Ann Arbor staging criteria (with cotswold modifications) were added to the protocol.</p> |
| 23 June 2017 | <p>a) Administrative changes related to the transfer of the compound from ImmunoGen Inc. to Debiopharm International S.A.</p> <p>b) Cohorts 1 and 2 were specified.</p> |
| 23 February 2018 | <p>a) Part 2 and Part 3 were introduced with the subject population restricted to r/r DLBCL who had responded to the last prior DLBCL systemic therapy and had achieved a duration of response (CR or PR) of at least 8 weeks (from the last day of the last cycle). Primary refractory subjects were excluded. The change was aimed at having a more homogeneous population for data analysis.</p> <p>b) A new once every week (QW) Debio 1562 dosing schedule (Cohort B) was added while maintaining the Q3W Debio 1562 dosing arm (Cohort A), without increasing the cumulative Debio 1562 dose currently allowed in the protocol (i.e., 0.7 mg/kg – 1.0 mg/kg Q3W).</p> <p>c) Cohort 1 (enrolling DLBCL with a huge proportion of primary refractory and refractory to last line subjects) and Cohort 2 (enrolling other NHL subjects) were stopped.</p> <p>d) The fixed study design was changed to an adaptive design to utilize the generated data to establish a dosing regimen associated with optimal benefit-risk.</p> <p>e) Blood sampling time points were added to improve evaluation of PK disposition</p> <p>f) Pharmacodynamic and drug metabolism enzymes and transporters (DMET) assessments were added</p> <p>g) Health-related quality of life (HRQoL) assessment was added.</p> |
| 19 December 2018 | <p>a) The eligibility criteria were updated to exclude subjects presenting interstitial lung disease, diffuse parenchymal lung disease, or with a past history of severe/Grade 3 parenchymal lung disorder</p> <p>b) The monitoring period was extended to 4 h after completion of the rituximab infusion for the first cycle</p> <p>c) A new section of risk minimization measures for the expected serious adverse reactions was introduced.</p> |

| | |
|------------------|--|
| 23 February 2020 | <p>a) The main reason for this amendment was to exceptionally allow treatment prolongation beyond 6 cycles, provided the subject is benefitting from the study drug.</p> <p>b) The following changes associated with treatment prolongation were added: imaging modality of radiologic tumor response assessments, timepoint of the last PK, immunogenicity, immunophenotyping, and HRQoL assessments</p> <p>c) Clarification that primary analysis will be conducted after all enrolled subject reach their 3rd on-treatment scheduled response assessment or they discontinue treatment, and that the final analysis will be triggered one year after the last accrued subject's first dose date. Clarification that the data from treatment prolongation will be summarized in an addendum.</p> <p>d) Clarification that the potential immunogenicity against rituximab will be assessed.</p> |
| 24 April 2020 | <p>This amendment was following an urgent safety measure during the COVID-19 pandemic to reduce risks to subjects visiting study sites. The main modification was to allow subjects on the QW Debio 1562 dosing regimen to switch to the Q3W dosing regimen to reduce the frequency of their visits to hospitals. This also entailed the addition of a sensitivity analysis for subjects who switched their treatment regimen.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported