



Clinical trial results:

A 12-month, open-label, multicenter, randomized, safety, efficacy, pharmacokinetic (PK) and pharmacodynamic (PD) study of two regimens of anti-CD40 monoclonal antibody, CFZ533 vs. standard of care control, in adult de novo liver transplant recipients with a 12-month additional follow-up and a long-term extension (CONTRAIL I)

Summary

| | |
|--------------------------|-------------------------|
| EudraCT number | 2018-001836-24 |
| Trial protocol | DE BE ES GB HU FR NL IT |
| Global end of trial date | 20 April 2023 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 |
| This version publication date | 04 April 2024 |
| First version publication date | 04 April 2024 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CCFZ533A2202 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03781414 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Novartis Pharma AG |
| Sponsor organisation address | Novartis Campus, Basel, Switzerland, |
| Public contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.com |
| Scientific contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.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 | 20 April 2023 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 20 April 2023 |
| Global end of trial reached? | Yes |
| Global end of trial date | 20 April 2023 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the rate of composite efficacy failure (Biopsy Proven Acute Rejection (BPAR), graft loss or death) with CFZ533 600 mg and 300 mg regimens compared to TAC Control at Month 12 post-transplantation. The primary objective would be demonstrated, if the composite efficacy failure rate difference between any of the two CFZ533 arms and the TAC arm is below to the pre-defined non-inferiority margin (0.15) with probability >80%. Hence, the primary endpoint was met for CFZ533 300 mg and was not met for CFZ533 600 mg.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 07 October 2019 |
| 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 | Argentina: 6 |
| Country: Number of subjects enrolled | Belgium: 3 |
| Country: Number of subjects enrolled | Czechia: 2 |
| Country: Number of subjects enrolled | France: 19 |
| Country: Number of subjects enrolled | Germany: 14 |
| Country: Number of subjects enrolled | Hungary: 6 |
| Country: Number of subjects enrolled | Italy: 19 |
| Country: Number of subjects enrolled | Netherlands: 1 |
| Country: Number of subjects enrolled | Spain: 8 |
| Country: Number of subjects enrolled | United States: 50 |
| Worldwide total number of subjects | 128 |
| EEA total number of subjects | 72 |

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) | 101 |
| From 65 to 84 years | 27 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The patients were enrolled at 3 sites in Argentina, 1 in Belgium, 1 in Czech Republic, 4 in France, 4 in Germany, 1 in Hungary, 1 in Italy, 1 in The Netherlands, 4 in Spain and 9 in United States.

Pre-assignment

Screening details:

Patients were randomized at a ratio of 2:3:3 to TAC Control (Arm 1) or one of two maintenance regimens of CFZ533: 600 mg CFZ533 subcutaneous (SC) injections every 2 weeks (Arm 2) or 300 mg CFZ533 SC injections every 2 weeks (Arm 3) combined with MMF and CS.

Period 1

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

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | Yes |
| Arm title | CFZ533 300 mg regimen (CFZ533 300 mg + MMF) |

Arm description:

Single loading dose of 30 mg/kg IV on Day 8 (with +/- 2 days window). The SC administration of 300 mg (1 injection of 2 mL CFZ533 at 150 mg/mL) every 2 weeks started on Day 29, in combination with MMF and CS up to EOS.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | CFZ533 300 mg |
| Investigational medicinal product code | |
| Other name | Iscalimab |
| Pharmaceutical forms | Solution for injection in pre-filled syringe, Solution for infusion in pre-filled syringe, Solution for injection/infusion in pre-filled syringe |
| Routes of administration | Subcutaneous use, Intravenous use |

Dosage and administration details:

Single loading dose of 30 mg/kg IV on Day 8 (with +/- 2 days window). The SC administration of 300 mg (1 injection of 2 mL CFZ533 at 150 mg/mL) every 2 weeks started on Day 29, in combination with Mycophenolate mofetil (MMF) + Corticosteroids (CS) up to EOS.

| | |
|------------------|---|
| Arm title | CFZ533 600 mg regimen (CFZ533 600 mg + MMF) |
|------------------|---|

Arm description:

Loading doses of 30 mg/kg IV on Day 8 (with +/- 2 days window), and 15 mg/kg IV on Day 15. The subcutaneous (SC) administration of 600 mg (2 injections of 2 mL CFZ533 at 150 mg/mL) every 2 weeks started on Day 29, in combination with MMF and CS up to EOS.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | CFZ533 600 mg |
| Investigational medicinal product code | |
| Other name | Iscalimab |
| Pharmaceutical forms | Solution for infusion in pre-filled syringe, Solution for injection in pre-filled syringe, Solution for injection/infusion in pre-filled syringe |
| Routes of administration | Intravenous use |

Dosage and administration details:

Loading doses of 30 mg/kg IV on Day 8 (with +/- 2 days window), and 15 mg/kg IV on Day 15. The SC administration of 600 mg (2 injections of 2 mL CFZ533 at 150 mg/mL) every 2 weeks started on Day 29, in combination with Mycophenolate mofetil (MMF) + Corticosteroids (CS) up to EOS.

| | |
|------------------|-------------------------|
| Arm title | TAC Control (TAC + MMF) |
|------------------|-------------------------|

Arm description:

Tacrolimus (TAC) + Mycophenolate mofetil (MMF) + Corticosteroids (CS) up to End of Study (EOS). Initial TAC target trough were between 5-15 ng/mL during the run-in period. From randomization onwards, the TAC levels were adjusted as per local label.

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | Tacrolimus (TAC) + Mycophenolate mofetil (MMF) + Corticosteroids (CS) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion in pre-filled syringe, Solution for injection in pre-filled syringe, Solution for injection/infusion in pre-filled syringe, Tablet |
| Routes of administration | Intravenous use, Subcutaneous use, Oral use |

Dosage and administration details:

Tacrolimus (TAC) + Mycophenolate mofetil (MMF) + Corticosteroids (CS) up to End of Study (EOS). Initial TAC target trough were between 5-15 ng/mL during the run-in period. From randomization onwards, the TAC levels were adjusted as per local label.

| Number of subjects in period 1 | CFZ533 300 mg regimen (CFZ533 300 mg + MMF) | CFZ533 600 mg regimen (CFZ533 600 mg + MMF) | TAC Control (TAC + MMF) |
|---------------------------------------|---|---|-------------------------|
| Started | 48 | 48 | 32 |
| Safety Set (SAF) | 48 | 47 | 32 |
| Completed | 0 | 0 | 0 |
| Not completed | 48 | 48 | 32 |
| Adverse event, serious fatal | 1 | 4 | - |
| Physician decision | 2 | - | 1 |
| Consent withdrawn by subject | 2 | 3 | 3 |
| Adverse event, non-fatal | 3 | 6 | 3 |
| Study terminated by sponsor | 39 | 34 | 25 |
| Lost to follow-up | 1 | 1 | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | CFZ533 300 mg regimen (CFZ533 300 mg + MMF) |
|-----------------------|---|

Reporting group description:

Single loading dose of 30 mg/kg IV on Day 8 (with +/- 2 days window). The SC administration of 300 mg (1 injection of 2 mL CFZ533 at 150 mg/mL) every 2 weeks started on Day 29, in combination with MMF and CS up to EOS.

| | |
|-----------------------|---|
| Reporting group title | CFZ533 600 mg regimen (CFZ533 600 mg + MMF) |
|-----------------------|---|

Reporting group description:

Loading doses of 30 mg/kg IV on Day 8 (with +/- 2 days window), and 15 mg/kg IV on Day 15. The subcutaneous (SC) administration of 600 mg (2 injections of 2 mL CFZ533 at 150 mg/mL) every 2 weeks started on Day 29, in combination with MMF and CS up to EOS.

| | |
|-----------------------|-------------------------|
| Reporting group title | TAC Control (TAC + MMF) |
|-----------------------|-------------------------|

Reporting group description:

Tacrolimus (TAC) + Mycophenolate mofetil (MMF) + Corticosteroids (CS) up to End of Study (EOS). Initial TAC target trough were between 5-15 ng/mL during the run-in period. From randomization onwards, the TAC levels were adjusted as per local label.

| Reporting group values | CFZ533 300 mg regimen (CFZ533 300 mg + MMF) | CFZ533 600 mg regimen (CFZ533 600 mg + MMF) | TAC Control (TAC + MMF) |
|--|---|---|-------------------------|
| Number of subjects | 48 | 48 | 32 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 36 | 39 | 26 |
| From 65-84 years | 12 | 9 | 6 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous | | | |
| Units: Years | | | |
| arithmetic mean | 56.7 | 56.2 | 54.0 |
| standard deviation | ± 9.94 | ± 6.98 | ± 9.90 |
| Sex: Female, Male | | | |
| Units: Participants | | | |
| Female | 11 | 15 | 8 |
| Male | 37 | 33 | 24 |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| White | 45 | 46 | 29 |
| Black or African American | 3 | 2 | 2 |
| Unknown | 0 | 0 | 1 |

| Reporting group values | Total | | |
|------------------------|-------|--|--|
| Number of subjects | 128 | | |

| | | | |
|---|-----|--|--|
| Age categorical Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | | |
| Newborns (0-27 days) | 0 | | |
| Infants and toddlers (28 days-23 months) | 0 | | |
| Children (2-11 years) | 0 | | |
| Adolescents (12-17 years) | 0 | | |
| Adults (18-64 years) | 101 | | |
| From 65-84 years | 27 | | |
| 85 years and over | 0 | | |
| Age Continuous Units: Years arithmetic mean standard deviation | - | | |
| Sex: Female, Male Units: Participants | | | |
| Female | 34 | | |
| Male | 94 | | |
| Race/Ethnicity, Customized Units: Subjects | | | |
| White | 120 | | |
| Black or African American | 7 | | |
| Unknown | 1 | | |

End points

End points reporting groups

| | |
|---|---|
| Reporting group title | CFZ533 300 mg regimen (CFZ533 300 mg + MMF) |
| Reporting group description: Single loading dose of 30 mg/kg IV on Day 8 (with +/- 2 days window). The SC administration of 300 mg (1 injection of 2 mL CFZ533 at 150 mg/mL) every 2 weeks started on Day 29, in combination with MMF and CS up to EOS. | |
| Reporting group title | CFZ533 600 mg regimen (CFZ533 600 mg + MMF) |
| Reporting group description: Loading doses of 30 mg/kg IV on Day 8 (with +/- 2 days window), and 15 mg/kg IV on Day 15. The subcutaneous (SC) administration of 600 mg (2 injections of 2 mL CFZ533 at 150 mg/mL) every 2 weeks started on Day 29, in combination with MMF and CS up to EOS. | |
| Reporting group title | TAC Control (TAC + MMF) |
| Reporting group description: Tacrolimus (TAC) + Mycophenolate mofetil (MMF) + Corticosteroids (CS) up to End of Study (EOS). Initial TAC target trough were between 5-15 ng/mL during the run-in period. From randomization onwards, the TAC levels were adjusted as per local label. | |

Primary: Proportion of patients with composite event (Biopsy Proven Acute Rejection (BPAR), Graft Loss or Death) over 12 months

| | |
|---|--|
| End point title | Proportion of patients with composite event (Biopsy Proven Acute Rejection (BPAR), Graft Loss or Death) over 12 months |
| End point description: The occurrence of biopsy proven acute rejection (BPAR) was evaluated based on central pathologist evaluation. Graft loss and death was evaluated as per local evaluation. | |
| End point type | Primary |
| End point timeframe: Baseline to Month 12 | |

| End point values | CFZ533 300 mg regimen (CFZ533 300 mg + MMF) | CFZ533 600 mg regimen (CFZ533 600 mg + MMF) | TAC Control (TAC + MMF) | |
|-----------------------------|---|---|-------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 48 | 48 | 32 | |
| Units: Participants | 8 | 12 | 3 | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Composite event (BPAR, Graft Loss or Death) |
| Comparison groups | CFZ533 600 mg regimen (CFZ533 600 mg + MMF) v TAC Control (TAC + MMF) |

| | |
|---|-----------------|
| Number of subjects included in analysis | 80 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Rate difference |
| Point estimate | 0.1696 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.0072 |
| upper limit | 0.3276 |

| | |
|---|---|
| Statistical analysis title | Composite event (BPAR, Graft Loss or Death) |
| Comparison groups | CFZ533 300 mg regimen (CFZ533 300 mg + MMF) v TAC Control (TAC + MMF) |
| Number of subjects included in analysis | 80 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Rate difference |
| Point estimate | 0.0759 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.0729 |
| upper limit | 0.2165 |

Secondary: Mean change in estimated Glomerular Filtration Rate (eGFR) from randomization to Month 12

| | |
|--|---|
| End point title | Mean change in estimated Glomerular Filtration Rate (eGFR) from randomization to Month 12 |
| End point description: Renal function as measured by estimated Glomerular Filtration Rate (eGFR) was evaluated using the MDRD formula (Levey et al 2006): $eGFR = 175 \times (\text{serum concentration of creatinine (SCr)})^{-1.154} \times (\text{age})^{-0.203} \times 0.742 [\text{if female}] \times 1.212 [\text{if Black}]$. | |
| End point type | Secondary |
| End point timeframe: Baseline to Month 12 | |

| End point values | CFZ533 300 mg regimen (CFZ533 300 mg + MMF) | CFZ533 600 mg regimen (CFZ533 600 mg + MMF) | TAC Control (TAC + MMF) | |
|--|---|---|-------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 48 | 48 | 32 | |
| Units: mL/min/1.73 m2 | | | | |
| arithmetic mean (full range (min-max)) | 2.05 (-60.4 to 71.5) | -9.31 (-55.8 to 28.7) | -14.74 (-104.0 to 20.6) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Treatment Emergent Adverse Events

| | |
|-----------------|---|
| End point title | Number of Participants with Treatment Emergent Adverse Events |
|-----------------|---|

End point description:

The distribution of adverse events was done via the analysis of frequencies for treatment emergent Adverse Event (TEAEs), Serious Adverse Event (TESAEs), Deaths due to AEs and TEAEs leading to discontinuation, through the monitoring of relevant clinical and laboratory safety parameters.

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

End point timeframe:

Baseline up to 14 weeks after last dose of study medication (CFZ533 participants) and until 12 weeks for TAC participants, up to approx. 184 weeks.

| End point values | CFZ533 300 mg regimen (CFZ533 300 mg + MMF) | CFZ533 600 mg regimen (CFZ533 600 mg + MMF) | TAC Control (TAC + MMF) | |
|----------------------------------|---|---|-------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 48 | 47 | 32 | |
| Units: Participants | | | | |
| TEAEs | 48 | 44 | 32 | |
| TESAEs | 30 | 29 | 20 | |
| Fatal TESAEs | 1 | 4 | 0 | |
| TEAEs leading to discontinuation | 14 | 17 | 8 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients with dose interruptions and permanent discontinuation of study treatment

| | |
|-----------------|---|
| End point title | Proportion of patients with dose interruptions and permanent discontinuation of study treatment |
|-----------------|---|

End point description:

The number and percentage of participants with dose changes (MMF and TAC), dose interruptions (only in cases of ascites drainage), and permanent discontinuation was summarized.

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

End point timeframe:

Baseline to Month 24

| End point values | CFZ533 300 mg regimen (CFZ533 300 mg + MMF) | CFZ533 600 mg regimen (CFZ533 600 mg + MMF) | TAC Control (TAC + MMF) | |
|---|---|---|-------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 48 | 47 | 32 | |
| Units: Participants | | | | |
| CFZ533: Subjects with dose interrupted | 8 | 5 | 999 | |
| CFZ533: Subjects with permanent d/c of study tx | 2 | 3 | 999 | |
| TAC: Subjects with dose interrupted | 3 | 3 | 6 | |
| TAC: Subjects with permanent d/c of study tx | 4 | 8 | 4 | |
| MMF: Subjects with dose interrupted | 18 | 23 | 15 | |
| MMF: Subjects with permanent d/c of study tx | 9 | 5 | 1 | |

Statistical analyses

No statistical analyses for this end point

Post-hoc: All collected deaths

| | |
|---|----------------------|
| End point title | All collected deaths |
| End point description: | |
| On-treatment deaths were reported from first dose of study treatment to 14 weeks after last dose of study medication (CFZ533 participants) and until 12 weeks for TAC participants, up to approx. 184 weeks. | |
| Post-treatment deaths were collected in the post treatment period from 15 weeks after last dose of study medication (CFZ533 participants, Arms 2 & 3) and from 13 weeks for TAC participants (Arm 1), up to approx. 184 weeks. These are not considered Adverse Events. | |
| End point type | Post-hoc |
| End point timeframe: | |
| On-treatment deaths: Up to approximately 184 weeks. Post-treatment deaths: Up to approximately 184 weeks. | |

| End point values | CFZ533 300 mg regimen (CFZ533 300 mg + MMF) | CFZ533 600 mg regimen (CFZ533 600 mg + MMF) | TAC Control (TAC + MMF) | |
|-----------------------------|---|---|-------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 48 | 47 | 32 | |
| Units: Participants | | | | |
| On-treatment deaths | 1 | 3 | 0 | |
| Post-treatment deaths | 0 | 1 | 0 | |
| All deaths | 1 | 4 | 0 | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment adverse events and deaths were reported from first dose of study treatment to 14 weeks after last dose of study medication (CFZ533 participants) and until 12 weeks for TAC participants, up to approx. 184 weeks.

Adverse event reporting additional description:

Any sign or symptom that occurred during the conduct of the trial and safety follow-up. The safety analysis were done on the safety population, which included all randomized subjects who received at least one dose of study medication.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 26.0 |
|--------------------|------|

Reporting groups

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|-----------------------|---------------------|
| Reporting group title | CFZ533 600 mg + MMF |
|-----------------------|---------------------|

Reporting group description:

CFZ533 600 mg + MMF

| | |
|-----------------------|-----------|
| Reporting group title | TAC + MMF |
|-----------------------|-----------|

Reporting group description:

TAC + MMF

| | |
|-----------------------|---------------------|
| Reporting group title | CFZ533 300 mg + MMF |
|-----------------------|---------------------|

Reporting group description:

CFZ533 300 mg + MMF

| Serious adverse events | CFZ533 600 mg + MMF | TAC + MMF | CFZ533 300 mg + MMF |
|---|---------------------|------------------|---------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 30 / 48 (62.50%) | 20 / 32 (62.50%) | 29 / 47 (61.70%) |
| number of deaths (all causes) | 1 | 0 | 3 |
| number of deaths resulting from adverse events | 0 | 0 | 2 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Metastases to lung | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 2 / 48 (4.17%) | 0 / 32 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholangiocarcinoma | | | |

| | | | |
|--|-----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant peritoneal neoplasm | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 1 / 32 (3.13%) | 0 / 47 (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 |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematoma | | | |
| subjects affected / exposed | 2 / 48 (4.17%) | 0 / 32 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Circulatory collapse | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 5 / 48 (10.42%) | 0 / 32 (0.00%) | 5 / 47 (10.64%) |
| occurrences causally related to treatment / all | 2 / 5 | 0 / 0 | 3 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |

| | | | |
|---|----------------|----------------|----------------|
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 1 / 32 (3.13%) | 0 / 47 (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 |
| Immune system disorders | | | |
| Graft versus host disease | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 32 (0.00%) | 2 / 47 (4.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Liver transplant rejection | | | |
| subjects affected / exposed | 2 / 48 (4.17%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transplant rejection | | | |
| subjects affected / exposed | 4 / 48 (8.33%) | 2 / 32 (6.25%) | 2 / 47 (4.26%) |
| occurrences causally related to treatment / all | 3 / 4 | 2 / 2 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (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 |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 48 (4.17%) | 0 / 32 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (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 |

| | | | |
|---|----------------|----------------|----------------|
| Pulmonary mass | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (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 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Interstitial lung disease | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (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 |
| Psychiatric disorders | | | |
| Suicide attempt | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 1 / 32 (3.13%) | 0 / 47 (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 |
| Mental status changes | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 32 (0.00%) | 2 / 47 (4.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hallucination | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Product issues | | | |

| | | | |
|---|----------------|----------------|----------------|
| Device dislocation subjects affected / exposed | 0 / 48 (0.00%) | 1 / 32 (3.13%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Carbohydrate antigen 19-9 increased subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood alkaline phosphatase increased subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic enzyme increased subjects affected / exposed | 0 / 48 (0.00%) | 1 / 32 (3.13%) | 3 / 47 (6.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 2 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Liver function test abnormal subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (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 |
| Liver function test increased subjects affected / exposed | 2 / 48 (4.17%) | 0 / 32 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Liver transplant failure subjects affected / exposed | 0 / 48 (0.00%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Incisional hernia subjects affected / exposed | 1 / 48 (2.08%) | 2 / 32 (6.25%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Graft loss | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 1 / 32 (3.13%) | 2 / 47 (4.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femoral neck fracture | | | |
| subjects affected / exposed | 2 / 48 (4.17%) | 0 / 32 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripancreatic fluid collection | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (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 |
| Complications of transplanted liver | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (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 |
| Biliary anastomosis complication | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 2 / 47 (4.26%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ankle fracture | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 1 / 32 (3.13%) | 0 / 47 (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 |
| Anastomotic stenosis | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 1 / 32 (3.13%) | 0 / 47 (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 |
| Fall | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 1 / 32 (3.13%) | 0 / 47 (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 pseudoaneurysm | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 32 (0.00%) | 2 / 47 (4.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ulna fracture | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Toxicity to various agents | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 1 / 32 (3.13%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thoracic vertebral fracture | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stress fracture | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (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 |
| Seroma | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural bile leak | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 1 / 32 (3.13%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Atrioventricular block | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (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 |
| Arteriosclerosis coronary artery | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 1 / 32 (3.13%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Supraventricular extrasystoles | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 1 / 32 (3.13%) | 0 / 47 (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 |
| Sinus arrhythmia | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 1 / 32 (3.13%) | 0 / 47 (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 |
| Nervous system disorders | | | |
| Lethargy | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 1 / 32 (3.13%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tremor | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukopenia | | | |
| subjects affected / exposed | 2 / 48 (4.17%) | 0 / 32 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Appendicitis noninfective | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (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 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (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 |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 48 (4.17%) | 1 / 32 (3.13%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ascites | | | |
| subjects affected / exposed | 2 / 48 (4.17%) | 2 / 32 (6.25%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diaphragmatic hernia | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematochezia | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enteritis | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 1 / 32 (3.13%) | 0 / 47 (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 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ileus | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (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 |
| Incarcerated umbilical hernia | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 1 / 32 (3.13%) | 0 / 47 (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 |
| Inguinal hernia strangulated | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (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 |
| Small intestinal obstruction | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 48 (0.00%) | 1 / 32 (3.13%) | 0 / 47 (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 |
| Varices oesophageal | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (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 |
| Salivary gland calculus | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (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 |
| Pancreatitis acute | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (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 |
| Large intestine perforation | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 1 / 32 (3.13%) | 0 / 47 (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 |
| Salivary gland enlargement | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (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 |
| Hepatobiliary disorders | | | |
| Cholangitis | | | |
| subjects affected / exposed | 2 / 48 (4.17%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Biloma | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (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 |
| Biliary tract disorder | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Biliary obstruction | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Biliary ischaemia | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bile duct stenosis | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholangitis acute | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 2 / 48 (4.17%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Hepatitis cholestatic | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (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 |
| Hepatic mass | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic artery stenosis | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 32 (0.00%) | 2 / 47 (4.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic haematoma | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (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 |
| Hepatic artery thrombosis | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic haemorrhage | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Jaundice | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 1 / 32 (3.13%) | 0 / 47 (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 |
| Skin and subcutaneous tissue disorders | | | |
| Petechiae | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rash | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Renal cyst ruptured | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (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 |
| Acute kidney injury | | | |
| subjects affected / exposed | 2 / 48 (4.17%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Abscess | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthritis bacterial | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| COVID-19 | | | |
| subjects affected / exposed | 4 / 48 (8.33%) | 2 / 32 (6.25%) | 2 / 47 (4.26%) |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (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 |
| Clostridium difficile colitis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 48 (0.00%) | 1 / 32 (3.13%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cytomegalovirus colitis | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cytomegalovirus hepatitis | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cytomegalovirus infection | | | |
| subjects affected / exposed | 3 / 48 (6.25%) | 0 / 32 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cytomegalovirus infection reactivation | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cytomegalovirus viraemia | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 1 / 32 (3.13%) | 2 / 47 (4.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endophthalmitis | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enterococcal infection | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia sepsis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (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 |
| Herpes zoster disseminated | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Liver abscess | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritonitis | | | |
| subjects affected / exposed | 2 / 48 (4.17%) | 1 / 32 (3.13%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Toxoplasmosis | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (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 |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound infection | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 32 (0.00%) | 2 / 47 (4.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritonitis bacterial | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 1 / 32 (3.13%) | 0 / 47 (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 |
| Pneumocystis jirovecii pneumonia | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 48 (4.17%) | 1 / 32 (3.13%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia cytomegaloviral | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (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 |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 1 / 32 (3.13%) | 0 / 47 (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 |
| Metabolism and nutrition disorders | | | |
| Hypervolaemia | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 48 (0.00%) | 1 / 32 (3.13%) | 0 / 47 (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 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 1 / 32 (3.13%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 1 / 32 (3.13%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 1 / 32 (3.13%) | 0 / 47 (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 |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | CFZ533 600 mg + MMF | TAC + MMF | CFZ533 300 mg + MMF |
|---|---------------------|------------------|---------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 45 / 48 (93.75%) | 30 / 32 (93.75%) | 42 / 47 (89.36%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 3 / 48 (6.25%) | 6 / 32 (18.75%) | 3 / 47 (6.38%) |
| occurrences (all) | 3 | 6 | 3 |
| Hypotension | | | |
| subjects affected / exposed | 3 / 48 (6.25%) | 1 / 32 (3.13%) | 2 / 47 (4.26%) |
| occurrences (all) | 3 | 1 | 2 |
| General disorders and administration site conditions | | | |

| | | | |
|--|------------------------|----------------------|-----------------------|
| Fatigue subjects affected / exposed occurrences (all) | 5 / 48 (10.42%) 7 | 5 / 32 (15.63%) 6 | 5 / 47 (10.64%) 5 |
| Asthenia subjects affected / exposed occurrences (all) | 2 / 48 (4.17%) 2 | 3 / 32 (9.38%) 3 | 2 / 47 (4.26%) 2 |
| Oedema peripheral subjects affected / exposed occurrences (all) | 12 / 48 (25.00%) 12 | 4 / 32 (12.50%) 4 | 6 / 47 (12.77%) 6 |
| Pyrexia subjects affected / exposed occurrences (all) | 7 / 48 (14.58%) 22 | 5 / 32 (15.63%) 5 | 8 / 47 (17.02%) 24 |
| Peripheral swelling subjects affected / exposed occurrences (all) | 1 / 48 (2.08%) 1 | 2 / 32 (6.25%) 2 | 1 / 47 (2.13%) 1 |
| Immune system disorders Liver transplant rejection subjects affected / exposed occurrences (all) | 1 / 48 (2.08%) 1 | 2 / 32 (6.25%) 2 | 1 / 47 (2.13%) 1 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 7 / 48 (14.58%) 9 | 0 / 32 (0.00%) 0 | 5 / 47 (10.64%) 7 |
| Dyspnoea subjects affected / exposed occurrences (all) | 4 / 48 (8.33%) 5 | 3 / 32 (9.38%) 3 | 5 / 47 (10.64%) 6 |
| Pleural effusion subjects affected / exposed occurrences (all) | 5 / 48 (10.42%) 5 | 3 / 32 (9.38%) 5 | 2 / 47 (4.26%) 2 |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 5 / 48 (10.42%) 5 | 2 / 32 (6.25%) 2 | 3 / 47 (6.38%) 3 |
| Alcoholism subjects affected / exposed occurrences (all) | 1 / 48 (2.08%) 1 | 0 / 32 (0.00%) 0 | 3 / 47 (6.38%) 3 |

| | | | |
|--|-----------------------|----------------------|----------------------|
| Insomnia subjects affected / exposed occurrences (all) | 6 / 48 (12.50%) 6 | 3 / 32 (9.38%) 3 | 3 / 47 (6.38%) 3 |
| Investigations | | | |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 2 / 48 (4.17%) 2 | 0 / 32 (0.00%) 0 | 3 / 47 (6.38%) 4 |
| Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) | 6 / 48 (12.50%) 6 | 1 / 32 (3.13%) 1 | 6 / 47 (12.77%) 6 |
| Blood creatinine increased subjects affected / exposed occurrences (all) | 1 / 48 (2.08%) 1 | 4 / 32 (12.50%) 4 | 0 / 47 (0.00%) 0 |
| Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all) | 4 / 48 (8.33%) 4 | 1 / 32 (3.13%) 1 | 2 / 47 (4.26%) 3 |
| Hepatic enzyme increased subjects affected / exposed occurrences (all) | 1 / 48 (2.08%) 1 | 2 / 32 (6.25%) 3 | 4 / 47 (8.51%) 4 |
| Liver function test increased subjects affected / exposed occurrences (all) | 8 / 48 (16.67%) 11 | 2 / 32 (6.25%) 2 | 4 / 47 (8.51%) 6 |
| Weight increased subjects affected / exposed occurrences (all) | 1 / 48 (2.08%) 1 | 0 / 32 (0.00%) 0 | 3 / 47 (6.38%) 3 |
| Injury, poisoning and procedural complications | | | |
| Overdose subjects affected / exposed occurrences (all) | 0 / 48 (0.00%) 0 | 2 / 32 (6.25%) 2 | 0 / 47 (0.00%) 0 |
| Contusion subjects affected / exposed occurrences (all) | 0 / 48 (0.00%) 0 | 2 / 32 (6.25%) 2 | 1 / 47 (2.13%) 1 |
| Cardiac disorders | | | |
| Palpitations subjects affected / exposed occurrences (all) | 0 / 48 (0.00%) 0 | 2 / 32 (6.25%) 2 | 1 / 47 (2.13%) 1 |

| | | | |
|--|------------------------|-----------------------|------------------------|
| Tachycardia subjects affected / exposed occurrences (all) | 2 / 48 (4.17%) 2 | 0 / 32 (0.00%) 0 | 4 / 47 (8.51%) 4 |
| Nervous system disorders | | | |
| Headache subjects affected / exposed occurrences (all) | 5 / 48 (10.42%) 6 | 7 / 32 (21.88%) 8 | 10 / 47 (21.28%) 11 |
| Syncope subjects affected / exposed occurrences (all) | 4 / 48 (8.33%) 4 | 0 / 32 (0.00%) 0 | 1 / 47 (2.13%) 1 |
| Tremor subjects affected / exposed occurrences (all) | 5 / 48 (10.42%) 6 | 7 / 32 (21.88%) 9 | 6 / 47 (12.77%) 6 |
| Blood and lymphatic system disorders | | | |
| Lymphopenia subjects affected / exposed occurrences (all) | 2 / 48 (4.17%) 2 | 1 / 32 (3.13%) 1 | 5 / 47 (10.64%) 5 |
| Neutropenia subjects affected / exposed occurrences (all) | 14 / 48 (29.17%) 18 | 4 / 32 (12.50%) 4 | 10 / 47 (21.28%) 12 |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 0 / 48 (0.00%) 0 | 3 / 32 (9.38%) 3 | 3 / 47 (6.38%) 3 |
| Anaemia subjects affected / exposed occurrences (all) | 4 / 48 (8.33%) 4 | 4 / 32 (12.50%) 4 | 5 / 47 (10.64%) 5 |
| Leukopenia subjects affected / exposed occurrences (all) | 17 / 48 (35.42%) 20 | 9 / 32 (28.13%) 11 | 16 / 47 (34.04%) 20 |
| Eye disorders | | | |
| Vision blurred subjects affected / exposed occurrences (all) | 3 / 48 (6.25%) 3 | 0 / 32 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Gastrointestinal disorders | | | |
| Constipation subjects affected / exposed occurrences (all) | 6 / 48 (12.50%) 7 | 4 / 32 (12.50%) 4 | 4 / 47 (8.51%) 4 |

| | | | |
|--|------------------|-----------------|-----------------|
| Diarrhoea | | | |
| subjects affected / exposed | 12 / 48 (25.00%) | 9 / 32 (28.13%) | 8 / 47 (17.02%) |
| occurrences (all) | 15 | 9 | 12 |
| Ascites | | | |
| subjects affected / exposed | 8 / 48 (16.67%) | 3 / 32 (9.38%) | 2 / 47 (4.26%) |
| occurrences (all) | 11 | 4 | 2 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 5 / 48 (10.42%) | 1 / 32 (3.13%) | 5 / 47 (10.64%) |
| occurrences (all) | 5 | 2 | 5 |
| Abdominal pain | | | |
| subjects affected / exposed | 5 / 48 (10.42%) | 8 / 32 (25.00%) | 7 / 47 (14.89%) |
| occurrences (all) | 6 | 10 | 7 |
| Abdominal distension | | | |
| subjects affected / exposed | 6 / 48 (12.50%) | 3 / 32 (9.38%) | 1 / 47 (2.13%) |
| occurrences (all) | 7 | 3 | 2 |
| Intra-abdominal fluid collection | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 2 / 32 (6.25%) | 1 / 47 (2.13%) |
| occurrences (all) | 1 | 3 | 1 |
| Vomiting | | | |
| subjects affected / exposed | 7 / 48 (14.58%) | 4 / 32 (12.50%) | 3 / 47 (6.38%) |
| occurrences (all) | 11 | 5 | 3 |
| Nausea | | | |
| subjects affected / exposed | 8 / 48 (16.67%) | 5 / 32 (15.63%) | 4 / 47 (8.51%) |
| occurrences (all) | 10 | 7 | 8 |
| Hepatobiliary disorders | | | |
| Cholangitis | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 2 / 32 (6.25%) | 1 / 47 (2.13%) |
| occurrences (all) | 1 | 2 | 1 |
| Bile duct stenosis | | | |
| subjects affected / exposed | 2 / 48 (4.17%) | 0 / 32 (0.00%) | 4 / 47 (8.51%) |
| occurrences (all) | 3 | 0 | 4 |
| Portal vein stenosis | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 2 / 32 (6.25%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Rash | | | |
| subjects affected / exposed | 3 / 48 (6.25%) | 1 / 32 (3.13%) | 5 / 47 (10.64%) |
| occurrences (all) | 3 | 1 | 5 |
| Actinic keratosis | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 3 / 32 (9.38%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Night sweats | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 32 (0.00%) | 3 / 47 (6.38%) |
| occurrences (all) | 1 | 0 | 3 |
| Pruritus | | | |
| subjects affected / exposed | 2 / 48 (4.17%) | 4 / 32 (12.50%) | 2 / 47 (4.26%) |
| occurrences (all) | 3 | 6 | 3 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 2 / 48 (4.17%) | 3 / 32 (9.38%) | 0 / 47 (0.00%) |
| occurrences (all) | 3 | 6 | 0 |
| Dysuria | | | |
| subjects affected / exposed | 4 / 48 (8.33%) | 1 / 32 (3.13%) | 1 / 47 (2.13%) |
| occurrences (all) | 4 | 1 | 1 |
| Haematuria | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 2 / 32 (6.25%) | 1 / 47 (2.13%) |
| occurrences (all) | 0 | 2 | 1 |
| Proteinuria | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 2 / 32 (6.25%) | 1 / 47 (2.13%) |
| occurrences (all) | 0 | 2 | 1 |
| Urinary incontinence | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 2 / 32 (6.25%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 9 / 48 (18.75%) | 2 / 32 (6.25%) | 6 / 47 (12.77%) |
| occurrences (all) | 11 | 2 | 6 |
| Back pain | | | |
| subjects affected / exposed | 8 / 48 (16.67%) | 4 / 32 (12.50%) | 5 / 47 (10.64%) |
| occurrences (all) | 8 | 4 | 5 |
| Flank pain | | | |

| | | | |
|---|------------------------|-----------------------|------------------------|
| subjects affected / exposed occurrences (all) | 0 / 48 (0.00%) 0 | 1 / 32 (3.13%) 1 | 3 / 47 (6.38%) 3 |
| Pain in extremity subjects affected / exposed occurrences (all) | 2 / 48 (4.17%) 2 | 2 / 32 (6.25%) 2 | 2 / 47 (4.26%) 2 |
| Muscle spasms subjects affected / exposed occurrences (all) | 0 / 48 (0.00%) 0 | 2 / 32 (6.25%) 2 | 1 / 47 (2.13%) 1 |
| Infections and infestations | | | |
| COVID-19 subjects affected / exposed occurrences (all) | 15 / 48 (31.25%) 15 | 8 / 32 (25.00%) 10 | 15 / 47 (31.91%) 16 |
| Cellulitis subjects affected / exposed occurrences (all) | 0 / 48 (0.00%) 0 | 2 / 32 (6.25%) 2 | 0 / 47 (0.00%) 0 |
| Cystitis subjects affected / exposed occurrences (all) | 1 / 48 (2.08%) 2 | 3 / 32 (9.38%) 3 | 2 / 47 (4.26%) 2 |
| Cytomegalovirus infection subjects affected / exposed occurrences (all) | 8 / 48 (16.67%) 8 | 4 / 32 (12.50%) 4 | 5 / 47 (10.64%) 8 |
| Cytomegalovirus infection reactivation subjects affected / exposed occurrences (all) | 2 / 48 (4.17%) 7 | 2 / 32 (6.25%) 5 | 5 / 47 (10.64%) 8 |
| Cytomegalovirus viraemia subjects affected / exposed occurrences (all) | 5 / 48 (10.42%) 10 | 2 / 32 (6.25%) 2 | 6 / 47 (12.77%) 7 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 1 / 48 (2.08%) 1 | 0 / 32 (0.00%) 0 | 3 / 47 (6.38%) 3 |
| Oral herpes subjects affected / exposed occurrences (all) | 0 / 48 (0.00%) 0 | 2 / 32 (6.25%) 2 | 1 / 47 (2.13%) 1 |
| Urinary tract infection | | | |

| | | | |
|------------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed | 4 / 48 (8.33%) | 7 / 32 (21.88%) | 4 / 47 (8.51%) |
| occurrences (all) | 9 | 8 | 6 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 2 / 32 (6.25%) | 1 / 47 (2.13%) |
| occurrences (all) | 1 | 2 | 1 |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 2 / 32 (6.25%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Metabolism and nutrition disorders | | | |
| Cell death | | | |
| subjects affected / exposed | 3 / 48 (6.25%) | 0 / 32 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Decreased appetite | | | |
| subjects affected / exposed | 2 / 48 (4.17%) | 0 / 32 (0.00%) | 3 / 47 (6.38%) |
| occurrences (all) | 2 | 0 | 3 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 2 / 48 (4.17%) | 2 / 32 (6.25%) | 2 / 47 (4.26%) |
| occurrences (all) | 2 | 2 | 2 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 2 / 48 (4.17%) | 4 / 32 (12.50%) | 2 / 47 (4.26%) |
| occurrences (all) | 2 | 5 | 2 |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 32 (0.00%) | 6 / 47 (12.77%) |
| occurrences (all) | 0 | 0 | 8 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 3 / 32 (9.38%) | 1 / 47 (2.13%) |
| occurrences (all) | 1 | 5 | 1 |
| Hypokalaemia | | | |
| subjects affected / exposed | 4 / 48 (8.33%) | 1 / 32 (3.13%) | 3 / 47 (6.38%) |
| occurrences (all) | 4 | 1 | 3 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 1 / 32 (3.13%) | 3 / 47 (6.38%) |
| occurrences (all) | 1 | 1 | 4 |
| Iron deficiency | | | |
| subjects affected / exposed | 3 / 48 (6.25%) | 1 / 32 (3.13%) | 0 / 47 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |

| | | | |
|--|---------------------|---------------------|---------------------|
| Vitamin D deficiency subjects affected / exposed occurrences (all) | 0 / 48 (0.00%) 0 | 2 / 32 (6.25%) 2 | 1 / 47 (2.13%) 1 |
|--|---------------------|---------------------|---------------------|

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|----------------|---|
| 09 July 2019 | Amendment 1 introduced optional liver biopsies to explore the effect of the study drugs on histology of the liver over time up to 12 months after transplant. |
| 05 March 2020 | Amendment 2 clarified that the stopping rule for biopsy proven acute rejection is based on moderate and severe events (Rejection Activity Index (RAI) ≥ 6) evaluated by a blinded central pathologist; introduced the change of the screening period from 6 months to 2 months; increased the visit window for the randomization visit at Day 8 from +/- 1 to +/- 2 days; and clarified inclusion/exclusion criteria. |
| 20 August 2020 | Amendment 3 introduced pre-filled syringes (PFS) to allow for self-administration after Month 12 visit, to offer more flexibility and improve adherence; and added three inclusion/exclusion criteria. The protocol amendment 3 also changed the LPLV date as at time of last EOS visit. However, per GCP the LPLV has to be at the end of the safety-FU period. For this reason, the LPLV date was changed to the end of safety-FU period. |
| 05 March 2021 | Amendment 4 allowed to increase the study duration by adding an extension period to collect long-term data in a controlled, clinical trial setting; clarified one exclusion criterion (history of coagulopathy); and added a new exclusion criterion (exclude donors with confirmed history of SARS-CoV-2 infection). |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com> for complete trial results.

Notes: