



## Clinical trial results:

### A Phase 3 Randomized Study of the Efficacy and Safety of Posaconazole versus Voriconazole for the Treatment of Invasive Aspergillosis in Adults and Adolescents (Phase 3; Protocol No. MK-5592-069)

#### Summary

|                          |                                              |
|--------------------------|----------------------------------------------|
| EudraCT number           | 2011-003938-14                               |
| Trial protocol           | ES DE BE LT PT GB EE IT PL GR FR HU CZ HR RO |
| Global end of trial date | 10 September 2019                            |

#### Results information

|                                |                   |
|--------------------------------|-------------------|
| Result version number          | v2 (current)      |
| This version publication date  | 26 September 2020 |
| First version publication date | 26 August 2020    |
| Version creation reason        |                   |

#### Trial information

##### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | P06200 |
|-----------------------|--------|

##### Additional study identifiers

|                                    |                                 |
|------------------------------------|---------------------------------|
| ISRCTN number                      | -                               |
| ClinicalTrials.gov id (NCT number) | NCT01782131                     |
| WHO universal trial number (UTN)   | -                               |
| Other trial identifiers            | Merck Registration: MK-5592-069 |

Notes:

#### Sponsors

|                              |                                                                                              |
|------------------------------|----------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Merck Sharp & Dohme Corp.                                                                    |
| Sponsor organisation address | 2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033                               |
| Public contact               | Clinical Trials Disclosure, Merck Sharp & Dohme Corp.,<br>ClinicalTrialsDisclosure@merck.com |
| Scientific contact           | Clinical Trials Disclosure, Merck Sharp & Dohme Corp.,<br>ClinicalTrialsDisclosure@merck.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? | Yes |

Notes:

## Results analysis stage

|                                                      |                   |
|------------------------------------------------------|-------------------|
| Analysis stage                                       | Final             |
| Date of interim/final analysis                       | 10 September 2019 |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 10 July 2019      |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 10 September 2019 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the safety and efficacy of posaconazole (POS) versus voriconazole (VOR) in the treatment of adults and adolescents with invasive aspergillosis (IA). The primary hypothesis is that the all-cause mortality through Day 42 in the POS treatment group is non-inferior to that in the VOR treatment group.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

|                                                           |                   |
|-----------------------------------------------------------|-------------------|
| Actual start date of recruitment                          | 25 September 2013 |
| 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: 84            |
| Country: Number of subjects enrolled | Brazil: 14             |
| Country: Number of subjects enrolled | Canada: 21             |
| Country: Number of subjects enrolled | Chile: 5               |
| Country: Number of subjects enrolled | China: 62              |
| Country: Number of subjects enrolled | Colombia: 51           |
| Country: Number of subjects enrolled | Czech Republic: 1      |
| Country: Number of subjects enrolled | Estonia: 3             |
| Country: Number of subjects enrolled | France: 11             |
| Country: Number of subjects enrolled | Germany: 33            |
| Country: Number of subjects enrolled | Hungary: 9             |
| Country: Number of subjects enrolled | Israel: 59             |
| Country: Number of subjects enrolled | Italy: 17              |
| Country: Number of subjects enrolled | Korea, Republic of: 39 |
| Country: Number of subjects enrolled | Mexico: 29             |
| Country: Number of subjects enrolled | Peru: 6                |
| Country: Number of subjects enrolled | Portugal: 2            |
| Country: Number of subjects enrolled | Romania: 1             |
| Country: Number of subjects enrolled | Russian Federation: 36 |

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Serbia: 4         |
| Country: Number of subjects enrolled | Singapore: 14     |
| Country: Number of subjects enrolled | Spain: 11         |
| Country: Number of subjects enrolled | Switzerland: 1    |
| Country: Number of subjects enrolled | Taiwan: 7         |
| Country: Number of subjects enrolled | Turkey: 30        |
| Country: Number of subjects enrolled | United States: 35 |
| Worldwide total number of subjects   | 585               |
| EEA total number of subjects         | 172               |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|-------------------------------------------|-----|
| 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)                 | 5   |
| Adults (18-64 years)                      | 417 |
| From 65 to 84 years                       | 161 |
| 85 years and over                         | 2   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

After a screening phase of up to 7 days, 585 participants were enrolled/randomized, but only 575 began treatment (288 in the posaconazole [POS] group and 287 in the voriconazole [VOR] group).

### Period 1

|                              |                                        |
|------------------------------|----------------------------------------|
| Period 1 title               | Randomization                          |
| Is this the baseline period? | No                                     |
| Allocation method            | Randomised - controlled                |
| Blinding used                | Double blind                           |
| Roles blinded                | Subject, Investigator, Assessor, Carer |

### Arms

|                              |              |
|------------------------------|--------------|
| Are arms mutually exclusive? | Yes          |
| <b>Arm title</b>             | Posaconazole |

Arm description:

Participants received 300 mg posaconazole (POS) intravenous (IV) twice per day (BID) on Day 1, and then received 300 mg POS IV plus placebo IV once per day (QD) starting on Day 2 until clinically stable when participants transitioned to oral POS tablets plus oral placebo tablets QD for up to 12 weeks of treatment. Most participants were expected to initiate treatment with IV therapy and transition to oral therapy as clinically indicated, with some participants initiating treatment with oral therapy, per clinical judgment.

|                                                           |                 |
|-----------------------------------------------------------|-----------------|
| Arm type                                                  | No intervention |
| No investigational medicinal product assigned in this arm |                 |
| <b>Arm title</b>                                          | Voriconazole    |

Arm description:

Participants received 6 mg/kg voriconazole (VOR) IV BID on Day 1, and then received 4 mg/kg VOR IV BID on Day 2 until clinically stable when participants transitioned to oral therapy with VOR capsules or VOR placebo capsules BID for up to 12 weeks of treatment. Most participants were expected to initiate treatment with IV therapy and transition to oral therapy as clinically indicated, with some participants initiating treatment with oral therapy, per clinical judgment.

|                                                           |                 |
|-----------------------------------------------------------|-----------------|
| Arm type                                                  | No intervention |
| No investigational medicinal product assigned in this arm |                 |

| Number of subjects in period 1 | Posaconazole | Voriconazole |
|--------------------------------|--------------|--------------|
| Started                        | 293          | 292          |
| Completed                      | 288          | 287          |
| Not completed                  | 5            | 5            |
| Randomized but not treated     | 5            | 5            |

**Period 2**

|                              |                                        |
|------------------------------|----------------------------------------|
| Period 2 title               | Treatment                              |
| Is this the baseline period? | Yes <sup>[1]</sup>                     |
| Allocation method            | Randomised - controlled                |
| Blinding used                | Double blind                           |
| Roles blinded                | Subject, Investigator, Carer, Assessor |

**Arms**

|                              |              |
|------------------------------|--------------|
| Are arms mutually exclusive? | Yes          |
| <b>Arm title</b>             | Posaconazole |

## Arm description:

Participants received 300 mg posaconazole (POS) intravenous (IV) twice per day (BID) on Day 1, and then received 300 mg POS IV plus placebo IV once per day (QD) starting on Day 2 until clinically stable when participants transitioned to oral POS tablets plus oral placebo tablets QD for up to 12 weeks of treatment. Most participants were expected to initiate treatment with IV therapy and transition to oral therapy as clinically indicated, with some participants initiating treatment with oral therapy, per clinical judgment.

|                                        |                             |
|----------------------------------------|-----------------------------|
| Arm type                               | Experimental                |
| Investigational medicinal product name | Posaconazole                |
| Investigational medicinal product code |                             |
| Other name                             | SCH 056592 MK-5592 Noxafil® |
| Pharmaceutical forms                   | Tablet, Infusion            |
| Routes of administration               | Oral use, Intravenous use   |

## Dosage and administration details:

POS IV: Day 1b: 300 mg BID, Day 2-84: 300 mg QD;

POS oral: Day 1b: 300 mg BID, Day 2-84: 300 mg QD

|                                        |                           |
|----------------------------------------|---------------------------|
| Investigational medicinal product name | Placebo                   |
| Investigational medicinal product code |                           |
| Other name                             |                           |
| Pharmaceutical forms                   | Infusion, Tablet          |
| Routes of administration               | Intravenous use, Oral use |

## Dosage and administration details:

Matching placebo received for Posaconazole

|                  |              |
|------------------|--------------|
| <b>Arm title</b> | Voriconazole |
|------------------|--------------|

## Arm description:

Participants received 6 mg/kg voriconazole (VOR) IV BID on Day 1, and then received 4 mg/kg VOR IV BID on Day 2 until clinically stable when participants transitioned to oral therapy with VOR capsules or VOR placebo capsules BID for up to 12 weeks of treatment. Most participants were expected to initiate treatment with IV therapy and transition to oral therapy as clinically indicated, with some participants initiating treatment with oral therapy, per clinical judgment.

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

## Dosage and administration details:

Matching placebo received for Voriconazole

|                                        |                           |
|----------------------------------------|---------------------------|
| Investigational medicinal product name | Voriconazole              |
| Investigational medicinal product code |                           |
| Other name                             | VFEND®                    |
| Pharmaceutical forms                   | Capsule, Infusion         |
| Routes of administration               | Oral use, Intravenous use |

---

**Dosage and administration details:**

VOR IV: Day 1b: 6 mg/kg per body weight administered BID,  
Day 2-84: 4 mg/kg per body weight administered BID;  
VOR oral: Day 1b: 300 mg BID, Day 2-84: 200 mg BID

---

**Notes:**

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

Justification: The All Patients as Treated population was used as the baseline population.

| <b>Number of subjects in period 2<sup>[2]</sup></b> | Posaconazole | Voriconazole |
|-----------------------------------------------------|--------------|--------------|
|                                                     |              |              |
| Started                                             | 288          | 287          |
| Completed                                           | 184          | 177          |
| Not completed                                       | 104          | 110          |
| Adverse event, serious fatal                        | 93           | 96           |
| Consent withdrawn by subject                        | 10           | 10           |
| Lost to follow-up                                   | 1            | 3            |
| Reason not provided                                 | -            | 1            |

---

**Notes:**

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

Justification: The All Patients as Treated population was used as the baseline population.

## Baseline characteristics

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Posaconazole |
|-----------------------|--------------|

Reporting group description:

Participants received 300 mg posaconazole (POS) intravenous (IV) twice per day (BID) on Day 1, and then received 300 mg POS IV plus placebo IV once per day (QD) starting on Day 2 until clinically stable when participants transitioned to oral POS tablets plus oral placebo tablets QD for up to 12 weeks of treatment. Most participants were expected to initiate treatment with IV therapy and transition to oral therapy as clinically indicated, with some participants initiating treatment with oral therapy, per clinical judgment.

|                       |              |
|-----------------------|--------------|
| Reporting group title | Voriconazole |
|-----------------------|--------------|

Reporting group description:

Participants received 6 mg/kg voriconazole (VOR) IV BID on Day 1, and then received 4 mg/kg VOR IV BID on Day 2 until clinically stable when participants transitioned to oral therapy with VOR capsules or VOR placebo capsules BID for up to 12 weeks of treatment. Most participants were expected to initiate treatment with IV therapy and transition to oral therapy as clinically indicated, with some participants initiating treatment with oral therapy, per clinical judgment.

| Reporting group values             | Posaconazole | Voriconazole | Total |
|------------------------------------|--------------|--------------|-------|
| Number of subjects                 | 288          | 287          | 575   |
| Age Categorical<br>Units: Subjects |              |              |       |

|                                                                         |                |                |     |
|-------------------------------------------------------------------------|----------------|----------------|-----|
| Age Continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 53.5<br>± 16.7 | 53.0<br>± 15.9 | -   |
| Gender Categorical<br>Units: Subjects                                   |                |                |     |
| Female                                                                  | 116            | 115            | 231 |
| Male                                                                    | 172            | 172            | 344 |
| Race<br>Units: Subjects                                                 |                |                |     |
| American Indian or Alaska Native                                        | 4              | 6              | 10  |
| Asian                                                                   | 62             | 60             | 122 |
| Black or African American                                               | 3              | 4              | 7   |
| Multiple                                                                | 25             | 25             | 50  |
| White                                                                   | 194            | 192            | 386 |
| Ethnicity<br>Units: Subjects                                            |                |                |     |
| Hispanic or Latino                                                      | 48             | 57             | 105 |
| Not Hispanic or Latino                                                  | 220            | 219            | 439 |
| Unknown or Not Reported                                                 | 20             | 11             | 31  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |              |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Posaconazole |
| Reporting group description:<br>Participants received 300 mg posaconazole (POS) intravenous (IV) twice per day (BID) on Day 1, and then received 300 mg POS IV plus placebo IV once per day (QD) starting on Day 2 until clinically stable when participants transitioned to oral POS tablets plus oral placebo tablets QD for up to 12 weeks of treatment. Most participants were expected to initiate treatment with IV therapy and transition to oral therapy as clinically indicated, with some participants initiating treatment with oral therapy, per clinical judgment. |              |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Voriconazole |
| Reporting group description:<br>Participants received 6 mg/kg voriconazole (VOR) IV BID on Day 1, and then received 4 mg/kg VOR IV BID on Day 2 until clinically stable when participants transitioned to oral therapy with VOR capsules or VOR placebo capsules BID for up to 12 weeks of treatment. Most participants were expected to initiate treatment with IV therapy and transition to oral therapy as clinically indicated, with some participants initiating treatment with oral therapy, per clinical judgment.                                                       |              |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Posaconazole |
| Reporting group description:<br>Participants received 300 mg posaconazole (POS) intravenous (IV) twice per day (BID) on Day 1, and then received 300 mg POS IV plus placebo IV once per day (QD) starting on Day 2 until clinically stable when participants transitioned to oral POS tablets plus oral placebo tablets QD for up to 12 weeks of treatment. Most participants were expected to initiate treatment with IV therapy and transition to oral therapy as clinically indicated, with some participants initiating treatment with oral therapy, per clinical judgment. |              |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Voriconazole |
| Reporting group description:<br>Participants received 6 mg/kg voriconazole (VOR) IV BID on Day 1, and then received 4 mg/kg VOR IV BID on Day 2 until clinically stable when participants transitioned to oral therapy with VOR capsules or VOR placebo capsules BID for up to 12 weeks of treatment. Most participants were expected to initiate treatment with IV therapy and transition to oral therapy as clinically indicated, with some participants initiating treatment with oral therapy, per clinical judgment.                                                       |              |

### Primary: Percentage of Participants Who Died Through Day 42 in the Intention to Treat Population

|                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                         |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                 | Percentage of Participants Who Died Through Day 42 in the Intention to Treat Population |
| End point description:<br>The percentage of participants who died with posaconazole (POS) compared to voriconazole (VOR) in the first line treatment of invasive aspergillosis (IA) in the Intention to Treat (ITT) population through Day 42 was assessed. The analysis population consisted of all randomized participants who received at least one dose of study treatment. |                                                                                         |
| End point type                                                                                                                                                                                                                                                                                                                                                                  | Primary                                                                                 |
| End point timeframe:<br>Up to ~42 days                                                                                                                                                                                                                                                                                                                                          |                                                                                         |

| End point values                  | Posaconazole    | Voriconazole    |  |  |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type                | Reporting group | Reporting group |  |  |
| Number of subjects analysed       | 288             | 287             |  |  |
| Units: Percentage of Participants |                 |                 |  |  |
| number (not applicable)           | 15.3            | 20.6            |  |  |

## Statistical analyses

| Statistical analysis title                                                                                                                                                                                                                                                                                                                                                | All-Cause Mortality by Day 42 in ITT |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|
| Statistical analysis description:                                                                                                                                                                                                                                                                                                                                         |                                      |
| Based on Miettinen and Nurminen's method stratified by the risk for mortality/poor outcome (high risk, not high risk) and using Cochran-Mantel-Haenszel weighting scheme. The p-Value is based on the one-sided non inferiority test. Non-inferiority of posaconazole vs. voriconazole is established if the upper limit of the 95% confidence interval is less than 10%. |                                      |
| Comparison groups                                                                                                                                                                                                                                                                                                                                                         | Voriconazole v Posaconazole          |
| Number of subjects included in analysis                                                                                                                                                                                                                                                                                                                                   | 575                                  |
| Analysis specification                                                                                                                                                                                                                                                                                                                                                    | Pre-specified                        |
| Analysis type                                                                                                                                                                                                                                                                                                                                                             | non-inferiority                      |
| P-value                                                                                                                                                                                                                                                                                                                                                                   | < 0.0001                             |
| Method                                                                                                                                                                                                                                                                                                                                                                    | Miettinen and Nurminen               |
| Parameter estimate                                                                                                                                                                                                                                                                                                                                                        | Estimated Difference in Percent      |
| Point estimate                                                                                                                                                                                                                                                                                                                                                            | -5.3                                 |
| Confidence interval                                                                                                                                                                                                                                                                                                                                                       |                                      |
| level                                                                                                                                                                                                                                                                                                                                                                     | 95 %                                 |
| sides                                                                                                                                                                                                                                                                                                                                                                     | 2-sided                              |
| lower limit                                                                                                                                                                                                                                                                                                                                                               | -11.6                                |
| upper limit                                                                                                                                                                                                                                                                                                                                                               | 1                                    |

## Secondary: Percentage of Participants Who Died Through Day 42 in the Full Analysis Set Population

| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Percentage of Participants Who Died Through Day 42 in the Full Analysis Set Population |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                        |
| The percentage of participants who died with POS compared to VOR in the first line treatment of invasive aspergillosis (IA) in the Full Analysis Set (FAS) population through Day 42 was assessed. The analysis population consisted of all randomized participants who have been classified as having proven or probable IA (based upon independent adjudication assessment using the modified 2008 European Organization for Research and Treatment of Cancer/Mycoses study group [EORTC/MSG] definitions) and received at least one dose of study drug. |                                                                                        |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Secondary                                                                              |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                        |
| Up to ~42 days                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                        |

| End point values                  | Posaconazole    | Voriconazole    |  |  |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type                | Reporting group | Reporting group |  |  |
| Number of subjects analysed       | 163             | 171             |  |  |
| Units: Percentage of Participants |                 |                 |  |  |
| number (not applicable)           | 19.0            | 18.7            |  |  |

## Statistical analyses

| Statistical analysis title                                                                                                                                                | All-Cause Mortality by Day 42 in FAS |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|
| Statistical analysis description:                                                                                                                                         |                                      |
| Based on Miettinen and Nurminen's method stratified by the risk for mortality/poor outcome (high risk, not high risk) and using Cochran-Mantel-Haenszel weighting scheme. |                                      |
| Comparison groups                                                                                                                                                         | Posaconazole v Voriconazole          |
| Number of subjects included in analysis                                                                                                                                   | 334                                  |
| Analysis specification                                                                                                                                                    | Pre-specified                        |
| Analysis type                                                                                                                                                             | other                                |
| Parameter estimate                                                                                                                                                        | Estimated Difference in Percent      |
| Point estimate                                                                                                                                                            | 0.3                                  |
| Confidence interval                                                                                                                                                       |                                      |
| level                                                                                                                                                                     | 95 %                                 |
| sides                                                                                                                                                                     | 2-sided                              |
| lower limit                                                                                                                                                               | -8.2                                 |
| upper limit                                                                                                                                                               | 8.8                                  |

## Secondary: Percentage of Participants Who Died Through Day 84 in the ITT Population

| End point title                                                                                                                                                                                                                                                                                                                  | Percentage of Participants Who Died Through Day 84 in the ITT Population |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| End point description:                                                                                                                                                                                                                                                                                                           |                                                                          |
| The percentage of participants who died with posaconazole (POS) compared to voriconazole (VOR) in the first line treatment of invasive aspergillosis (IA) in the ITT population through Day 84 was assessed. The analysis population consisted of all randomized participants who received at least one dose of study treatment. |                                                                          |
| End point type                                                                                                                                                                                                                                                                                                                   | Secondary                                                                |
| End point timeframe:                                                                                                                                                                                                                                                                                                             |                                                                          |
| Up to ~84 days                                                                                                                                                                                                                                                                                                                   |                                                                          |

| End point values                  | Posaconazole    | Voriconazole    |  |  |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type                | Reporting group | Reporting group |  |  |
| Number of subjects analysed       | 288             | 287             |  |  |
| Units: Percentage of Participants |                 |                 |  |  |
| number (not applicable)           | 28.1            | 30.7            |  |  |

## Statistical analyses

|                                                                                                                                                                                                                |                                      |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                              | All-Cause Mortality by Day 84 in ITT |
| Statistical analysis description:<br>Based on Miettinen and Nurminen's method stratified by the risk for mortality/poor outcome (high risk, not high risk) and using Cochran-Mantel-Haenszel weighting scheme. |                                      |
| Comparison groups                                                                                                                                                                                              | Posaconazole v Voriconazole          |
| Number of subjects included in analysis                                                                                                                                                                        | 575                                  |
| Analysis specification                                                                                                                                                                                         | Pre-specified                        |
| Analysis type                                                                                                                                                                                                  | other                                |
| Parameter estimate                                                                                                                                                                                             | Estimated Difference in Percent      |
| Point estimate                                                                                                                                                                                                 | -2.5                                 |
| Confidence interval                                                                                                                                                                                            |                                      |
| level                                                                                                                                                                                                          | 95 %                                 |
| sides                                                                                                                                                                                                          | 2-sided                              |
| lower limit                                                                                                                                                                                                    | -9.9                                 |
| upper limit                                                                                                                                                                                                    | 4.9                                  |

## Secondary: Percentage of Participants Who Died Through Day 84 in the FAS Population

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                          |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Percentage of Participants Who Died Through Day 84 in the FAS Population |
| End point description:<br>The percentage of participants who died with POS compared to VOR in the first line treatment of invasive aspergillosis (IA) in the FAS population through Day 84 was assessed. The analysis population consisted of all randomized participants who have been classified as having proven or probable IA (based upon independent adjudication assessment using the modified 2008 European Organization for Research and Treatment of Cancer/Mycoses study group [EORTC/MSG] definitions) and received at least one dose of study drug. |                                                                          |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Secondary                                                                |
| End point timeframe:<br>Up to ~84 days                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                          |

|                                   |                 |                 |  |  |
|-----------------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>           | Posaconazole    | Voriconazole    |  |  |
| Subject group type                | Reporting group | Reporting group |  |  |
| Number of subjects analysed       | 163             | 171             |  |  |
| Units: Percentage of Participants |                 |                 |  |  |
| number (not applicable)           | 34.4            | 31.0            |  |  |

## Statistical analyses

|                                                                                                                                                                                                                |                                      |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                              | All-Cause Mortality by Day 84 in FAS |
| Statistical analysis description:<br>Based on Miettinen and Nurminen's method stratified by the risk for mortality/poor outcome (high risk, not high risk) and using Cochran-Mantel-Haenszel weighting scheme. |                                      |
| Comparison groups                                                                                                                                                                                              | Posaconazole v Voriconazole          |
| Number of subjects included in analysis                                                                                                                                                                        | 334                                  |
| Analysis specification                                                                                                                                                                                         | Pre-specified                        |
| Analysis type                                                                                                                                                                                                  | other                                |
| Parameter estimate                                                                                                                                                                                             | Difference in Percent                |
| Point estimate                                                                                                                                                                                                 | 3.1                                  |
| Confidence interval                                                                                                                                                                                            |                                      |
| level                                                                                                                                                                                                          | 95 %                                 |
| sides                                                                                                                                                                                                          | 2-sided                              |
| lower limit                                                                                                                                                                                                    | -6.9                                 |
| upper limit                                                                                                                                                                                                    | 13.1                                 |

## Secondary: Percentage of Participants Achieving Global Clinical Response at Week 12 in the FAS Population

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Percentage of Participants Achieving Global Clinical Response at Week 12 in the FAS Population |
| End point description:<br>The global clinical response of posaconazole (POS) compared to voriconazole (VOR) in the first line treatment of invasive aspergillosis (IA) was assessed. The percentage of participants achieving adjudicated complete and partial global clinical response at Week 12 was reported. Complete response was classified as survival with resolution of fungal disease evidence; Partial response was survival and improvement of fungal disease. The analysis population consisted of all randomized participants who have been classified as having proven or probable IA (based upon independent adjudication assessment using the modified 2008 European Organization for Research and Treatment of Cancer/Mycoses Study Group [EORTC/MSG] definitions) and received at least one dose of study drug. |                                                                                                |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Secondary                                                                                      |
| End point timeframe:<br>Up to 12 weeks ( $\pm$ 4 weeks)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                |

|                                   |                 |                 |  |  |
|-----------------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>           | Posaconazole    | Voriconazole    |  |  |
| Subject group type                | Reporting group | Reporting group |  |  |
| Number of subjects analysed       | 163             | 171             |  |  |
| Units: Percentage of Participants |                 |                 |  |  |
| number (not applicable)           | 42.3            | 46.2            |  |  |

## Statistical analyses

|                                                                                                                                                                                                                |                                            |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                              | Global Clinical Response at Week 12 in FAS |
| Statistical analysis description:<br>Based on Miettinen and Nurminen's method stratified by the risk for mortality/poor outcome (high risk, not high risk) and using Cochran-Mantel-Haenszel weighting scheme. |                                            |

|                                         |                                 |
|-----------------------------------------|---------------------------------|
| Comparison groups                       | Posaconazole v Voriconazole     |
| Number of subjects included in analysis | 334                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | other                           |
| Parameter estimate                      | Estimated Difference in Percent |
| Point estimate                          | -3.4                            |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | -13.9                           |
| upper limit                             | 7.1                             |

## Secondary: Percentage of Participants Achieving Global Clinical Response at Week 6 in the FAS Population

|                 |                                                                                               |
|-----------------|-----------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants Achieving Global Clinical Response at Week 6 in the FAS Population |
|-----------------|-----------------------------------------------------------------------------------------------|

End point description:

The global clinical response of posaconazole (POS) compared to voriconazole (VOR) in the first line treatment of invasive aspergillosis (IA) was assessed. The percentage of participants achieving adjudicated complete and partial global clinical response at Week 6 was reported. Complete response was classified as survival with resolution of fungal disease evidence; Partial response was survival and improvement of fungal disease. The analysis population consisted of all randomized participants who have been classified as having proven or probable IA (based upon independent adjudication assessment using the modified 2008 European Organization for Research and Treatment of Cancer/Mycoses Study Group [EORTC/MSG] definitions) and received at least one dose of study drug.

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

End point timeframe:

Up to 6 weeks ( $\pm$  2 weeks)

| End point values                  | Posaconazole    | Voriconazole    |  |  |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type                | Reporting group | Reporting group |  |  |
| Number of subjects analysed       | 163             | 171             |  |  |
| Units: Percentage of Participants |                 |                 |  |  |
| number (not applicable)           | 44.8            | 45.6            |  |  |

## Statistical analyses

|                            |                                           |
|----------------------------|-------------------------------------------|
| Statistical analysis title | Global Clinical Response at Week 6 in FAS |
|----------------------------|-------------------------------------------|

Statistical analysis description:

Based on Miettinen and Nurminen's method stratified by the risk for mortality/poor outcome (high risk, not high risk) and using Cochran-Mantel-Haenszel weighting scheme.

|                   |                             |
|-------------------|-----------------------------|
| Comparison groups | Posaconazole v Voriconazole |
|-------------------|-----------------------------|

|                                         |                                 |
|-----------------------------------------|---------------------------------|
| Number of subjects included in analysis | 334                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | other                           |
| Parameter estimate                      | Estimated Difference in Percent |
| Point estimate                          | -0.6                            |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | -11.2                           |
| upper limit                             | 10.1                            |

### Secondary: Number of Participants Experiencing Mortality at Day 42, Day 84, and Day 114 in the FAS Population (Kaplan-Meier Time To Death Estimate)

|                 |                                                                                                                                          |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants Experiencing Mortality at Day 42, Day 84, and Day 114 in the FAS Population (Kaplan-Meier Time To Death Estimate) |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------|

#### End point description:

The number of participants experiencing mortality at Day 42, Day 84 and Day 114 in participants with proven or probable IA receiving POS versus VOR were assessed. The Kaplan-Meier estimate reports the number of participants who experienced death (all causes) through Day 114 or ~16 weeks. Participants who did not have any endpoint event until last visit or who were lost to follow-up and had no event were censored at the time of last available information (last study visit). For Day 42 and Day 84, missing or 'unable to determine' responses were considered as failures (dead). The analysis population consisted of all randomized participants who have been classified as having proven or probable IA (based upon independent adjudication assessment using the modified 2008 European Organization for Research and Treatment of Cancer/Mycoses study group [EORTC/MSG] definitions) and received at least one dose of study drug.

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

#### End point timeframe:

Up to ~16 weeks (± 2 weeks)

| End point values                                 | Posaconazole    | Voriconazole    |  |  |
|--------------------------------------------------|-----------------|-----------------|--|--|
| Subject group type                               | Reporting group | Reporting group |  |  |
| Number of subjects analysed                      | 163             | 171             |  |  |
| Units: Participants                              |                 |                 |  |  |
| number (not applicable)                          |                 |                 |  |  |
| Day 42 (missing responses were included as dead) | 31              | 32              |  |  |
| Day 84 (missing responses were included as dead) | 56              | 53              |  |  |
| Day 114                                          | 64              | 56              |  |  |

### Statistical analyses

|                            |                             |
|----------------------------|-----------------------------|
| Statistical analysis title | Time to Death, All Causes   |
| Comparison groups          | Posaconazole v Voriconazole |

|                                         |                          |
|-----------------------------------------|--------------------------|
| Number of subjects included in analysis | 334                      |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | other <sup>[1]</sup>     |
| P-value                                 | = 0.2767 <sup>[2]</sup>  |
| Method                                  | Kaplan-Meier             |
| Parameter estimate                      | Survival Rate in Percent |
| Point estimate                          | 60.7                     |
| Confidence interval                     |                          |
| level                                   | 95 %                     |
| sides                                   | 2-sided                  |
| lower limit                             | 52.8                     |
| upper limit                             | 67.8                     |

Notes:

[1] - From product-limit (Kaplan-Meier) method for censored data.

[2] - Based on Stratified Log-Rank method stratified by the risk for mortality/poor outcome (high risk, not high risk).

### Secondary: Number of Participants Who Died Due to Invasive Aspergillosis Through Day 42 in the FAS Population

|                 |                                                                                                    |
|-----------------|----------------------------------------------------------------------------------------------------|
| End point title | Number of Participants Who Died Due to Invasive Aspergillosis Through Day 42 in the FAS Population |
|-----------------|----------------------------------------------------------------------------------------------------|

End point description:

The number of participants who died due to IA receiving POS versus VOR through Day 42 was assessed. The analysis population consisted of all randomized participants who died by Day 42 and who have been classified as having proven or probable IA (based upon independent adjudication assessment using the modified 2008 European Organization for Research and Treatment of Cancer/Mycoses study group [EORTC/MSG] definitions), and received at least one dose of study drug.

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

End point timeframe:

Up to 42 days

| End point values            | Posaconazole    | Voriconazole    |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 31              | 32              |  |  |
| Units: Participants         |                 |                 |  |  |
| number (not applicable)     | 16              | 10              |  |  |

### Statistical analyses

|                            |                                 |
|----------------------------|---------------------------------|
| Statistical analysis title | Died due to IA by Day 42 in FAS |
|----------------------------|---------------------------------|

Statistical analysis description:

Based on Miettinen and Nurminen's method.

|                   |                             |
|-------------------|-----------------------------|
| Comparison groups | Posaconazole v Voriconazole |
|-------------------|-----------------------------|

|                                         |                       |
|-----------------------------------------|-----------------------|
| Number of subjects included in analysis | 63                    |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | other                 |
| Parameter estimate                      | Difference in Percent |
| Point estimate                          | 20.4                  |
| Confidence interval                     |                       |
| level                                   | 95 %                  |
| sides                                   | 2-sided               |
| lower limit                             | -4.1                  |
| upper limit                             | 42.7                  |

### Secondary: Number of Participants Who Died Due to Invasive Aspergillosis Through Day 84 in the FAS Population

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                    |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Number of Participants Who Died Due to Invasive Aspergillosis Through Day 84 in the FAS Population |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                    |
| The number of participants who died due to IA receiving POS versus VOR in the FAS population through Day 84 was assessed. The analysis population consisted of all randomized participants who died by Day 84 and who have been classified as having proven or probable IA (based upon independent adjudication assessment using the modified 2008 European Organization for Research and Treatment of Cancer/Mycoses study group [EORTC/MSG] definitions), and received at least one dose of study drug. |                                                                                                    |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Secondary                                                                                          |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                    |
| Up to 84 days                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                    |

| End point values            | Posaconazole    | Voriconazole    |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 56              | 50              |  |  |
| Units: Participants         |                 |                 |  |  |
| number (not applicable)     | 22              | 14              |  |  |

### Statistical analyses

|                                           |                                 |
|-------------------------------------------|---------------------------------|
| Statistical analysis title                | Died due to IA by Day 84 in FAS |
| Statistical analysis description:         |                                 |
| Based on Miettinen and Nurminen's method. |                                 |
| Comparison groups                         | Posaconazole v Voriconazole     |
| Number of subjects included in analysis   | 106                             |
| Analysis specification                    | Pre-specified                   |
| Analysis type                             | other                           |
| Parameter estimate                        | Difference in Percent           |
| Point estimate                            | 11.3                            |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -6.9    |
| upper limit         | 28.6    |

## Secondary: Percentage of Participants with Tier 1 Treatment Emergent Adverse Events

|                 |                                                                          |
|-----------------|--------------------------------------------------------------------------|
| End point title | Percentage of Participants with Tier 1 Treatment Emergent Adverse Events |
|-----------------|--------------------------------------------------------------------------|

End point description:

The percentage of participants with Tier 1 treatment-emergent adverse events (TEAEs) was determined. The Tier 1 TEAEs included hepatic safety (elevated aspartate serum transaminase [AST] or alanine serum transaminase [ALT] value  $\geq 3\times$  upper limit of normal (ULN) and an elevated total bilirubin value  $\geq 2\times$  ULN and, at the same time, an alkaline phosphatase value  $< 2$  ULN); central nervous system (CNS) and visual disturbances (eye disorders, nervous system disorders, psychiatric disorders), dermatologic reactions, and adrenal insufficiency or temporally associated TEAEs of hypotension. The analysis population consisted of all participants who received at least one dose of study treatment.

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

End point timeframe:

Up to ~16 weeks ( $\pm 2$  weeks)

| End point values                              | Posaconazole    | Voriconazole    |  |  |
|-----------------------------------------------|-----------------|-----------------|--|--|
| Subject group type                            | Reporting group | Reporting group |  |  |
| Number of subjects analysed                   | 288             | 287             |  |  |
| Units: Percentage of Participants             |                 |                 |  |  |
| number (not applicable)                       |                 |                 |  |  |
| Abnormal Hepatic Laboratory Value             | 3.8             | 3.5             |  |  |
| CNS and Visual Disturbances                   | 32.3            | 35.9            |  |  |
| Dermatologic Reactions                        | 16.3            | 19.2            |  |  |
| Adrenal Insufficiency or Temporal Hypotension | 8.0             | 7.0             |  |  |

## Statistical analyses

|                                         |                                   |
|-----------------------------------------|-----------------------------------|
| Statistical analysis title              | Abnormal Hepatic Laboratory Value |
| Comparison groups                       | Posaconazole v Voriconazole       |
| Number of subjects included in analysis | 575                               |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | other                             |
| P-value                                 | = 0.8305                          |
| Method                                  | Miettinen & Nurminen              |
| Parameter estimate                      | Difference in Percent             |
| Point estimate                          | 0.3                               |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -2.9    |
| upper limit         | 3.6     |

|                                         |                             |
|-----------------------------------------|-----------------------------|
| <b>Statistical analysis title</b>       | CNS and Visual Disturbances |
| Comparison groups                       | Posaconazole v Voriconazole |
| Number of subjects included in analysis | 575                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | other                       |
| P-value                                 | = 0.3633                    |
| Method                                  | Miettinen & Nurminen        |
| Parameter estimate                      | Difference in Percent       |
| Point estimate                          | -3.6                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | -11.3                       |
| upper limit                             | 4.2                         |

|                                         |                             |
|-----------------------------------------|-----------------------------|
| <b>Statistical analysis title</b>       | Dermatologic Reactions      |
| Comparison groups                       | Posaconazole v Voriconazole |
| Number of subjects included in analysis | 575                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | other                       |
| P-value                                 | = 0.3724                    |
| Method                                  | Miettinen & Nurminen        |
| Parameter estimate                      | Difference in Percent       |
| Point estimate                          | -2.8                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | -9.1                        |
| upper limit                             | 3.4                         |

|                                   |                                               |
|-----------------------------------|-----------------------------------------------|
| <b>Statistical analysis title</b> | Adrenal Insufficiency or Temporal Hypotension |
| Comparison groups                 | Posaconazole v Voriconazole                   |

|                                         |                       |
|-----------------------------------------|-----------------------|
| Number of subjects included in analysis | 575                   |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | other                 |
| P-value                                 | = 0.6431              |
| Method                                  | Miettinen & Nurminen  |
| Parameter estimate                      | Difference in Percent |
| Point estimate                          | 1                     |
| Confidence interval                     |                       |
| level                                   | 95 %                  |
| sides                                   | 2-sided               |
| lower limit                             | -3.4                  |
| upper limit                             | 5.5                   |

## Secondary: Percentage of Participants with at Least One Adverse Event

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                            |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Percentage of Participants with at Least One Adverse Event |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                            |
| An adverse event (AE) was defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which did not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product. The analysis population consisted of all randomized participants who received at least one dose of study treatment. |                                                            |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Secondary                                                  |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                            |
| Up to ~16 weeks ( $\pm$ 2 weeks)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                            |

| End point values                  | Posaconazole    | Voriconazole    |  |  |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type                | Reporting group | Reporting group |  |  |
| Number of subjects analysed       | 288             | 287             |  |  |
| Units: Percentage of Participants |                 |                 |  |  |
| number (not applicable)           | 97.6            | 97.6            |  |  |

## Statistical analyses

|                                         |                             |
|-----------------------------------------|-----------------------------|
| <b>Statistical analysis title</b>       | One or More Adverse Events  |
| Comparison groups                       | Posaconazole v Voriconazole |
| Number of subjects included in analysis | 575                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | other                       |
| Method                                  | Miettinen & Nurminen        |
| Parameter estimate                      | Difference in Percent       |
| Point estimate                          | 0                           |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -2.8    |
| upper limit         | 2.8     |

## Secondary: Percentage of Participants with at Least One Drug Related Adverse Event

|                 |                                                                         |
|-----------------|-------------------------------------------------------------------------|
| End point title | Percentage of Participants with at Least One Drug Related Adverse Event |
|-----------------|-------------------------------------------------------------------------|

End point description:

An AE was defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product. The analysis population consisted of all randomized participants who received at least one dose of study treatment.

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

End point timeframe:

Up to ~16 weeks ( $\pm$  2 weeks)

| End point values                  | Posaconazole    | Voriconazole    |  |  |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type                | Reporting group | Reporting group |  |  |
| Number of subjects analysed       | 288             | 287             |  |  |
| Units: Percentage of Participants |                 |                 |  |  |
| number (not applicable)           | 29.9            | 40.1            |  |  |

## Statistical analyses

|                                         |                             |
|-----------------------------------------|-----------------------------|
| Statistical analysis title              | Drug-Related Adverse Events |
| Comparison groups                       | Posaconazole v Voriconazole |
| Number of subjects included in analysis | 575                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | other                       |
| Method                                  | Miettinen & Nurminen        |
| Parameter estimate                      | Difference in Percent       |
| Point estimate                          | -10.2                       |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | -17.9                       |
| upper limit                             | -2.4                        |

**Secondary: Percentage of Participants with at Least One Serious Adverse Event**

|                 |                                                                    |
|-----------------|--------------------------------------------------------------------|
| End point title | Percentage of Participants with at Least One Serious Adverse Event |
|-----------------|--------------------------------------------------------------------|

End point description:

A serious adverse event (SAE) was an AE that resulted in death, was life threatening, required or prolonged an existing hospitalization, resulted in persistent or significant disability or incapacity, was a congenital anomaly or birth defect, or was another important medical event deemed such by medical or scientific judgment. The analysis population consisted of all randomized participants who received at least one dose of study treatment.

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

End point timeframe:

Up to ~16 weeks ( $\pm$  2 weeks)

|                                   |                 |                 |  |  |
|-----------------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>           | Posaconazole    | Voriconazole    |  |  |
| Subject group type                | Reporting group | Reporting group |  |  |
| Number of subjects analysed       | 288             | 287             |  |  |
| Units: Percentage of Participants |                 |                 |  |  |
| number (not applicable)           | 61.8            | 59.9            |  |  |

**Statistical analyses**

|                                         |                             |
|-----------------------------------------|-----------------------------|
| <b>Statistical analysis title</b>       | Serious Adverse Events      |
| Comparison groups                       | Posaconazole v Voriconazole |
| Number of subjects included in analysis | 575                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | other                       |
| Method                                  | Miettinen & Nurminen        |
| Parameter estimate                      | Difference in Percent       |
| Point estimate                          | 1.9                         |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | -6.1                        |
| upper limit                             | 9.8                         |

**Secondary: Percentage of Participants with at Least One Serious Drug-Related Adverse Event**

|                 |                                                                                 |
|-----------------|---------------------------------------------------------------------------------|
| End point title | Percentage of Participants with at Least One Serious Drug-Related Adverse Event |
|-----------------|---------------------------------------------------------------------------------|

End point description:

An SAE was an AE that resulted in death, was life threatening, required or prolonged an existing hospitalization, resulted in persistent or significant disability or incapacity, was a congenital anomaly or birth defect, or was another important medical event deemed such by medical or scientific judgment. The analysis population consisted of all randomized participants who received at least one dose of study treatment.

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

End point timeframe:

Up to ~16 weeks ( $\pm$  2 weeks)

|                                   |                 |                 |  |  |
|-----------------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>           | Posaconazole    | Voriconazole    |  |  |
| Subject group type                | Reporting group | Reporting group |  |  |
| Number of subjects analysed       | 288             | 287             |  |  |
| Units: Percentage of Participants |                 |                 |  |  |
| number (not applicable)           | 5.6             | 7.0             |  |  |

### Statistical analyses

|                                         |                                     |
|-----------------------------------------|-------------------------------------|
| <b>Statistical analysis title</b>       | Serious Drug-Related Adverse Events |
| Comparison groups                       | Posaconazole v Voriconazole         |
| Number of subjects included in analysis | 575                                 |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | other                               |
| Method                                  | Miettinen & Nurminen                |
| Parameter estimate                      | Difference in Percent               |
| Point estimate                          | -1.4                                |
| Confidence interval                     |                                     |
| level                                   | 95 %                                |
| sides                                   | 2-sided                             |
| lower limit                             | -5.6                                |
| upper limit                             | 2.7                                 |

### Secondary: Percentage of Participants who Discontinued Study Treatment due to an Adverse Event

|                 |                                                                                     |
|-----------------|-------------------------------------------------------------------------------------|
| End point title | Percentage of Participants who Discontinued Study Treatment due to an Adverse Event |
|-----------------|-------------------------------------------------------------------------------------|

End point description:

An AE was defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which did not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product. The analysis population consisted of all randomized participants who received at least one dose of study treatment.

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

End point timeframe:

Up to ~12 weeks

| End point values                  | Posaconazole    | Voriconazole    |  |  |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type                | Reporting group | Reporting group |  |  |
| Number of subjects analysed       | 288             | 287             |  |  |
| Units: Percentage of Participants |                 |                 |  |  |
| number (not applicable)           | 32.3            | 35.5            |  |  |

## Statistical analyses

| Statistical analysis title              | Discontinued due to an Adverse Event |
|-----------------------------------------|--------------------------------------|
| Comparison groups                       | Posaconazole v Voriconazole          |
| Number of subjects included in analysis | 575                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           | other                                |
| Method                                  | Miettinen & Nurminen                 |
| Parameter estimate                      | Difference in Percent                |
| Point estimate                          | -3.2                                 |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | -11                                  |
| upper limit                             | 4.5                                  |

## Secondary: Steady State Average Concentration (Cavg) of Posaconazole with Food Intake

|                 |                                                                                           |
|-----------------|-------------------------------------------------------------------------------------------|
| End point title | Steady State Average Concentration (Cavg) of Posaconazole with Food Intake <sup>[3]</sup> |
|-----------------|-------------------------------------------------------------------------------------------|

### End point description:

The characterization of the pharmacokinetics (PK) parameters of POS was determined from plasma samples taken at steady-state after receiving oral tablet of POS. Steady-state Cavg, where Cavg is defined as area under the concentration time-curve from 0 to 24 hours (AUC0-24hr) divided by the dosing interval. No evaluation of food intake on the VOR capsule was presented. The analysis population consisted of all randomized participants in the POS group only who received at least one dose of study treatment. Per protocol, the VOR group was not included in the analysis population because the food intake evaluation was limited to the POS group.

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

### End point timeframe:

Baseline, and at pre-dose on Day 7, Week 2, Week 4, Week 6, and Week 12

### Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The VOR group was not included in the analysis population because the food intake evaluation was limited to the POS group only.

| End point values                     | Posaconazole    |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| Subject group type                   | Reporting group |  |  |  |
| Number of subjects analysed          | 288             |  |  |  |
| Units: ng/mL                         |                 |  |  |  |
| arithmetic mean (standard deviation) |                 |  |  |  |
| Week 1: N=58                         | 1625 (± 902.9)  |  |  |  |

|               |                     |  |  |  |
|---------------|---------------------|--|--|--|
| Week 2: N=64  | 1992 ( $\pm$ 1190)  |  |  |  |
| Week 4: N=67  | 1994 ( $\pm$ 956.3) |  |  |  |
| Week 6: N=65  | 2005 ( $\pm$ 1333)  |  |  |  |
| Week 12: N=49 | 2169 ( $\pm$ 1255)  |  |  |  |

### Statistical analyses

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to ~16 weeks ( $\pm$  2 weeks)

Adverse event reporting additional description:

The analysis population consisted of all participants who received at least one dose of study treatment. The analysis population for the all-cause mortality included all randomized participants (n=293, n=292).

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 22.1 |
|--------------------|------|

### Reporting groups

|                       |                           |
|-----------------------|---------------------------|
| Reporting group title | Posaconazole (POS)-300 mg |
|-----------------------|---------------------------|

Reporting group description:

Participants received posaconazole intravenously (IV) twice per day (BID) on Day 1, and then received posaconazole IV once per day (QD) starting on Day 2 until clinically stable when participants transitioned to oral posaconazole tablets QD for up to 12 weeks of treatment. Participants with renal insufficiency or without central venous catheter access started with posaconazole oral tablets BID on Day 1, and then QD for up to 12 weeks of treatment.

|                       |                                      |
|-----------------------|--------------------------------------|
| Reporting group title | Voriconazole (VOR)-6 mg, 4 mg/200 mg |
|-----------------------|--------------------------------------|

Reporting group description:

Participants received voriconazole IV BID on Day 1, and then received voriconazole IV BID on Day 2 until clinically stable when participants transitioned to oral therapy with voriconazole capsules BID for up to 12 weeks of treatment. Participants with renal insufficiency or without central venous catheter access started treatment with oral voriconazole capsules BID on Day 1, and then BID for up to 12 weeks of treatment.

| Serious adverse events                                              | Posaconazole (POS)-300 mg | Voriconazole (VOR)-6 mg, 4 mg/200 mg |  |
|---------------------------------------------------------------------|---------------------------|--------------------------------------|--|
| Total subjects affected by serious adverse events                   |                           |                                      |  |
| subjects affected / exposed                                         | 178 / 288 (61.81%)        | 172 / 287 (59.93%)                   |  |
| number of deaths (all causes)                                       | 99                        | 99                                   |  |
| number of deaths resulting from adverse events                      | 0                         | 3                                    |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                           |                                      |  |
| Acute lymphocytic leukaemia                                         |                           |                                      |  |
| subjects affected / exposed                                         | 3 / 288 (1.04%)           | 1 / 287 (0.35%)                      |  |
| occurrences causally related to treatment / all                     | 0 / 3                     | 0 / 1                                |  |
| deaths causally related to treatment / all                          | 0 / 3                     | 0 / 1                                |  |
| Acute lymphocytic leukaemia recurrent                               |                           |                                      |  |
| subjects affected / exposed                                         | 3 / 288 (1.04%)           | 3 / 287 (1.05%)                      |  |
| occurrences causally related to treatment / all                     | 0 / 3                     | 0 / 3                                |  |
| deaths causally related to treatment / all                          | 0 / 2                     | 0 / 1                                |  |

|                                                 |                 |                  |  |
|-------------------------------------------------|-----------------|------------------|--|
| Acute myeloid leukaemia                         |                 |                  |  |
| subjects affected / exposed                     | 7 / 288 (2.43%) | 12 / 287 (4.18%) |  |
| occurrences causally related to treatment / all | 0 / 7           | 0 / 12           |  |
| deaths causally related to treatment / all      | 0 / 6           | 0 / 12           |  |
| Acute myeloid leukaemia recurrent               |                 |                  |  |
| subjects affected / exposed                     | 2 / 288 (0.69%) | 0 / 287 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| B-cell lymphoma recurrent                       |                 |                  |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| B-cell type acute leukaemia                     |                 |                  |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1            |  |
| Blast crisis in myelogenous leukaemia           |                 |                  |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Chronic lymphocytic leukaemia                   |                 |                  |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 2 / 287 (0.70%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1            |  |
| Diffuse large B-cell lymphoma                   |                 |                  |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0            |  |
| Diffuse large B-cell lymphoma refractory        |                 |                  |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0            |  |
| Hepatic cancer                                  |                 |                  |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Leukaemia recurrent                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lymphocytic leukaemia                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Lymphoma                                        |                 |                 |  |
| subjects affected / exposed                     | 2 / 288 (0.69%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Malignant neoplasm progression                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Myelodysplastic syndrome                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Neuroendocrine tumour of the lung               |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Non-Hodgkin's lymphoma                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 2 / 287 (0.70%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Plasma cell myeloma                             |                 |                 |  |

|                                                         |                 |                 |  |
|---------------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                             | 2 / 288 (0.69%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all         | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all              | 0 / 1           | 0 / 1           |  |
| Precursor T-lymphoblastic lymphoma/leukaemia refractory |                 |                 |  |
| subjects affected / exposed                             | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all         | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all              | 0 / 1           | 0 / 0           |  |
| Primary mediastinal large B-cell lymphoma               |                 |                 |  |
| subjects affected / exposed                             | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all         | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all              | 0 / 0           | 0 / 0           |  |
| Prostate cancer                                         |                 |                 |  |
| subjects affected / exposed                             | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all         | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all              | 0 / 0           | 0 / 0           |  |
| Tumour associated fever                                 |                 |                 |  |
| subjects affected / exposed                             | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all         | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all              | 0 / 0           | 0 / 0           |  |
| Vascular disorders                                      |                 |                 |  |
| Aortic aneurysm                                         |                 |                 |  |
| subjects affected / exposed                             | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all         | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all              | 0 / 0           | 0 / 0           |  |
| Deep vein thrombosis                                    |                 |                 |  |
| subjects affected / exposed                             | 1 / 288 (0.35%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all         | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all              | 0 / 0           | 0 / 0           |  |
| Hypotension                                             |                 |                 |  |
| subjects affected / exposed                             | 3 / 288 (1.04%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all         | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all              | 0 / 0           | 0 / 0           |  |
| Shock                                                   |                 |                 |  |

|                                                      |                 |                 |  |
|------------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                          | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Asthenia                                             |                 |                 |  |
| subjects affected / exposed                          | 1 / 288 (0.35%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Death                                                |                 |                 |  |
| subjects affected / exposed                          | 2 / 288 (0.69%) | 2 / 287 (0.70%) |  |
| occurrences causally related to treatment / all      | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all           | 0 / 2           | 0 / 2           |  |
| General physical health deterioration                |                 |                 |  |
| subjects affected / exposed                          | 1 / 288 (0.35%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 1           |  |
| Hypothermia                                          |                 |                 |  |
| subjects affected / exposed                          | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Mucosal inflammation                                 |                 |                 |  |
| subjects affected / exposed                          | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Multiple organ dysfunction syndrome                  |                 |                 |  |
| subjects affected / exposed                          | 0 / 288 (0.00%) | 3 / 287 (1.05%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 2           |  |
| Oedema                                               |                 |                 |  |
| subjects affected / exposed                          | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Pain                                                 |                 |                 |  |

|                                                     |                 |                 |  |
|-----------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                         | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all     | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all          | 0 / 0           | 0 / 0           |  |
| Pyrexia                                             |                 |                 |  |
| subjects affected / exposed                         | 7 / 288 (2.43%) | 5 / 287 (1.74%) |  |
| occurrences causally related to treatment / all     | 0 / 9           | 0 / 5           |  |
| deaths causally related to treatment / all          | 0 / 0           | 0 / 0           |  |
| Immune system disorders                             |                 |                 |  |
| Acute graft versus host disease                     |                 |                 |  |
| subjects affected / exposed                         | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all     | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all          | 0 / 1           | 0 / 0           |  |
| Acute graft versus host disease in skin             |                 |                 |  |
| subjects affected / exposed                         | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all     | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all          | 0 / 0           | 0 / 0           |  |
| Engraftment syndrome                                |                 |                 |  |
| subjects affected / exposed                         | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all     | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all          | 0 / 1           | 0 / 0           |  |
| Graft versus host disease in gastrointestinal tract |                 |                 |  |
| subjects affected / exposed                         | 2 / 288 (0.69%) | 2 / 287 (0.70%) |  |
| occurrences causally related to treatment / all     | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all          | 0 / 1           | 0 / 0           |  |
| Graft versus host disease in liver                  |                 |                 |  |
| subjects affected / exposed                         | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all     | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all          | 0 / 0           | 0 / 0           |  |
| Haemophagocytic lymphohistiocytosis                 |                 |                 |  |
| subjects affected / exposed                         | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all     | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all          | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Immune reconstitution inflammatory syndrome     |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Kidney transplant rejection                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Acute pulmonary oedema                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Acute respiratory distress syndrome             |                 |                 |  |
| subjects affected / exposed                     | 3 / 288 (1.04%) | 2 / 287 (0.70%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| Acute respiratory failure                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 3 / 287 (1.05%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Aspiration                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chronic obstructive pulmonary disease           |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Dyspnoea                                        |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Epistaxis                                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 288 (0.69%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemoptysis                                     |                 |                 |  |
| subjects affected / exposed                     | 4 / 288 (1.39%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0           |  |
| Hypoxia                                         |                 |                 |  |
| subjects affected / exposed                     | 3 / 288 (1.04%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Interstitial lung disease                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Lung disorder                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung infiltration                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Pneumonia aspiration                            |                 |                 |  |
| subjects affected / exposed                     | 2 / 288 (0.69%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonitis                                     |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumothorax                                    |                 |                 |  |
| subjects affected / exposed                     | 2 / 288 (0.69%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary alveolar haemorrhage                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 288 (0.69%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| Pulmonary artery thrombosis                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Pulmonary cavitation                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 2 / 287 (0.70%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary congestion                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary embolism                              |                 |                 |  |
| subjects affected / exposed                     | 2 / 288 (0.69%) | 2 / 287 (0.70%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Pulmonary haemorrhage                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 3 / 287 (1.05%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 3           |  |
| Pulmonary oedema                                |                 |                 |  |

|                                                 |                  |                 |  |
|-------------------------------------------------|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 288 (0.35%)  | 4 / 287 (1.39%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Respiratory disorder                            |                  |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%)  | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Respiratory distress                            |                  |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%)  | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Respiratory failure                             |                  |                 |  |
| subjects affected / exposed                     | 10 / 288 (3.47%) | 7 / 287 (2.44%) |  |
| occurrences causally related to treatment / all | 0 / 10           | 0 / 8           |  |
| deaths causally related to treatment / all      | 0 / 8            | 0 / 4           |  |
| Psychiatric disorders                           |                  |                 |  |
| Bipolar I disorder                              |                  |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%)  | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Confusional state                               |                  |                 |  |
| subjects affected / exposed                     | 2 / 288 (0.69%)  | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hallucination                                   |                  |                 |  |
| subjects affected / exposed                     | 2 / 288 (0.69%)  | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 2 / 2            | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Mental status changes                           |                  |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%)  | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Suicide attempt                                 |                  |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Investigations</b>                           |                 |                 |  |
| Alanine aminotransferase increased              |                 |                 |  |
| subjects affected / exposed                     | 3 / 288 (1.04%) | 3 / 287 (1.05%) |  |
| occurrences causally related to treatment / all | 3 / 3           | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Aspartate aminotransferase increased            |                 |                 |  |
| subjects affected / exposed                     | 2 / 288 (0.69%) | 2 / 287 (0.70%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood alkaline phosphatase increased            |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood creatinine increased                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood lactate dehydrogenase increased           |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cytomegalovirus test positive                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gamma-glutamyltransferase increased             |                 |                 |  |
| subjects affected / exposed                     | 2 / 288 (0.69%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                              |                 |                 |  |
|--------------------------------------------------------------|-----------------|-----------------|--|
| Liver function test increased<br>subjects affected / exposed | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to<br>treatment / all           | 0 / 0           | 1 / 1           |  |
| deaths causally related to<br>treatment / all                | 0 / 0           | 0 / 0           |  |
| Neutrophil count decreased<br>subjects affected / exposed    | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to<br>treatment / all           | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                | 0 / 0           | 0 / 0           |  |
| Transaminases increased<br>subjects affected / exposed       | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to<br>treatment / all           | 0 / 0           | 1 / 1           |  |
| deaths causally related to<br>treatment / all                | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural<br>complications            |                 |                 |  |
| Concussion<br>subjects affected / exposed                    | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to<br>treatment / all           | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                | 0 / 0           | 0 / 0           |  |
| Hip fracture<br>subjects affected / exposed                  | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to<br>treatment / all           | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                | 0 / 0           | 0 / 0           |  |
| Procedural pneumothorax<br>subjects affected / exposed       | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to<br>treatment / all           | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                | 0 / 0           | 0 / 0           |  |
| Spinal compression fracture<br>subjects affected / exposed   | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to<br>treatment / all           | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                | 0 / 0           | 0 / 0           |  |
| Subdural haematoma<br>subjects affected / exposed            | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to<br>treatment / all           | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                | 0 / 0           | 0 / 0           |  |

|                                                               |                 |                 |  |
|---------------------------------------------------------------|-----------------|-----------------|--|
| Thoracic vertebral fracture<br>subjects affected / exposed    | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to<br>treatment / all            | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                 | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                                             |                 |                 |  |
| Accessory cardiac pathway<br>subjects affected / exposed      | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to<br>treatment / all            | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                 | 0 / 0           | 0 / 0           |  |
| Acute coronary syndrome<br>subjects affected / exposed        | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to<br>treatment / all            | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                 | 0 / 1           | 0 / 0           |  |
| Acute left ventricular failure<br>subjects affected / exposed | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to<br>treatment / all            | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                 | 0 / 0           | 0 / 0           |  |
| Angina pectoris<br>subjects affected / exposed                | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to<br>treatment / all            | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                 | 0 / 0           | 0 / 0           |  |
| Arrhythmia<br>subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to<br>treatment / all            | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                 | 0 / 0           | 0 / 1           |  |
| Atrial fibrillation<br>subjects affected / exposed            | 4 / 288 (1.39%) | 2 / 287 (0.70%) |  |
| occurrences causally related to<br>treatment / all            | 0 / 4           | 0 / 2           |  |
| deaths causally related to<br>treatment / all                 | 0 / 0           | 0 / 0           |  |
| Cardiac arrest<br>subjects affected / exposed                 | 1 / 288 (0.35%) | 1 / 287 (0.35%) |  |
| occurrences causally related to<br>treatment / all            | 0 / 1           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                 | 0 / 1           | 0 / 1           |  |
| Cardiac failure                                               |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 288 (0.69%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Cardiac failure acute                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure congestive                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Left ventricular failure                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Myocardial infarction                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ventricular extrasystoles                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ventricular fibrillation                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Brain oedema                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 2 / 287 (0.70%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Cerebral disorder                               |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| Cerebral haemorrhage                            |                 |                 |  |
| subjects affected / exposed                     | 2 / 288 (0.69%) | 2 / 287 (0.70%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 1           |  |
| Cerebral infarction                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebrovascular accident                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dizziness                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Encephalopathy                                  |                 |                 |  |
| subjects affected / exposed                     | 3 / 288 (1.04%) | 5 / 287 (1.74%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 3 / 5           |  |
| deaths causally related to treatment / all      | 0 / 1           | 1 / 1           |  |
| Haemorrhage intracranial                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| Headache                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoaesthesia                                   |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Paraesthesia                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Seizure                                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 2 / 287 (0.70%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Status epilepticus                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Syncope                                         |                 |                 |  |
| subjects affected / exposed                     | 2 / 288 (0.69%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Transient ischaemic attack                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wernicke's encephalopathy                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders            |                 |                 |  |
| Anaemia                                         |                 |                 |  |
| subjects affected / exposed                     | 2 / 288 (0.69%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood disorder                                  |                 |                 |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 288 (0.35%)  | 0 / 287 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bone marrow failure                             |                  |                  |  |
| subjects affected / exposed                     | 3 / 288 (1.04%)  | 2 / 287 (0.70%)  |  |
| occurrences causally related to treatment / all | 1 / 3            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Febrile neutropenia                             |                  |                  |  |
| subjects affected / exposed                     | 24 / 288 (8.33%) | 21 / 287 (7.32%) |  |
| occurrences causally related to treatment / all | 0 / 32           | 0 / 26           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Leukopenia                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 288 (0.00%)  | 1 / 287 (0.35%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neutropenia                                     |                  |                  |  |
| subjects affected / exposed                     | 2 / 288 (0.69%)  | 1 / 287 (0.35%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancytopenia                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 288 (0.00%)  | 1 / 287 (0.35%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thrombocytopenia                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 288 (0.35%)  | 1 / 287 (0.35%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thrombotic thrombocytopenic purpura             |                  |                  |  |
| subjects affected / exposed                     | 1 / 288 (0.35%)  | 1 / 287 (0.35%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Eye disorders                                   |                  |                  |  |
| Vision blurred                                  |                  |                  |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |
| Abdominal distension                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal pain                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 288 (0.69%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal pain upper                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Colitis                                         |                 |                 |  |
| subjects affected / exposed                     | 2 / 288 (0.69%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diarrhoea                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 2 / 287 (0.70%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Duodenitis                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastric varices haemorrhage                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Gastritis                                       |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorder                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal haemorrhage                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 3 / 287 (1.05%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Gastrointestinal hypomotility                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ileus                                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Inflammatory bowel disease                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intestinal obstruction                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Melaena                                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nausea                                          |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 288 (0.00%) | 2 / 287 (0.70%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neutropenic colitis                             |                 |                 |  |
| subjects affected / exposed                     | 2 / 288 (0.69%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oesophageal ulcer                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| Rectal haemorrhage                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Small intestinal obstruction                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Stomatitis                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Upper gastrointestinal haemorrhage              |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vomiting                                        |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Cholangitis                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholecystitis                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholecystitis acute                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 2 / 287 (0.70%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatic cirrhosis                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatic function abnormal                       |                 |                 |  |
| subjects affected / exposed                     | 3 / 288 (1.04%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 2 / 3           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatocellular injury                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatotoxicity                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 2 / 287 (0.70%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hydrocholecystis                                |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperbilirubinaemia                             |                 |                 |  |
| subjects affected / exposed                     | 2 / 288 (0.69%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |                 |                 |  |
| Dermatitis exfoliative generalised              |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rash maculo-papular                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Toxic skin eruption                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Acute kidney injury                             |                 |                 |  |
| subjects affected / exposed                     | 9 / 288 (3.13%) | 5 / 287 (1.74%) |  |
| occurrences causally related to treatment / all | 1 / 9           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Cystitis haemorrhagic                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haematuria                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue           |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| disorders                                       |                 |                 |  |
| Arthralgia                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Back pain                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Muscle twitching                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal pain                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Abdominal abscess                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal sepsis                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Anal infection                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Appendicitis                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Aspergillus infection                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 2 / 287 (0.70%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 2           |  |
| Atypical pneumonia                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bacteraemia                                     |                 |                 |  |
| subjects affected / exposed                     | 5 / 288 (1.74%) | 3 / 287 (1.05%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0           |  |
| Bacterial pericarditis                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bacterial sepsis                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Brain abscess                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Bronchopulmonary aspergillosis                  |                 |                 |  |
| subjects affected / exposed                     | 6 / 288 (2.08%) | 6 / 287 (2.09%) |  |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 6           |  |
| deaths causally related to treatment / all      | 0 / 4           | 0 / 3           |  |
| Candida sepsis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Cellulitis                                      |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cellulitis pharyngeal                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Cerebral aspergillosis                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Citrobacter sepsis                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Clostridial infection                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Clostridium difficile colitis                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 2 / 287 (0.70%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Clostridium difficile infection                 |                 |                 |  |
| subjects affected / exposed                     | 2 / 288 (0.69%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Corona virus infection                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cystitis viral                                  |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cytomegalovirus infection                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 288 (0.69%) | 2 / 287 (0.70%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cytomegalovirus viraemia                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Device related infection                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Device related sepsis                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Disseminated cytomegaloviral infection          |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Diverticulitis                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Emphysematous cholecystitis                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Endocarditis                                    |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Endocarditis bacterial                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Enteritis infectious                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Enterobacter pneumonia                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 2 / 287 (0.70%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Enterobacter sepsis                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Enterococcal bacteraemia                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Enterococcal sepsis                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Escherichia bacteraemia                         |                 |                 |  |
| subjects affected / exposed                     | 3 / 288 (1.04%) | 2 / 287 (0.70%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Escherichia sepsis                              |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 288 (0.00%) | 2 / 287 (0.70%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Febrile infection                               |                 |                 |  |
| subjects affected / exposed                     | 2 / 288 (0.69%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Fungal infection                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Gastroenteritis norovirus                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatosplenic candidiasis                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Herpes zoster                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infection                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infectious pleural effusion                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Influenza                                       |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 3 / 288 (1.04%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intervertebral discitis                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Klebsiella bacteraemia                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 3 / 287 (1.05%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Klebsiella sepsis                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Lower respiratory tract infection bacterial     |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Lower respiratory tract infection viral         |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Meningitis                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mucormycosis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Muscle abscess                                  |                 |                 |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 288 (0.35%)  | 0 / 287 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neutropenic sepsis                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 288 (0.00%)  | 1 / 287 (0.35%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nocardiosis                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 288 (0.00%)  | 1 / 287 (0.35%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peritonitis                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 288 (0.35%)  | 0 / 287 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pneumocystis jirovecii pneumonia                |                  |                  |  |
| subjects affected / exposed                     | 1 / 288 (0.35%)  | 1 / 287 (0.35%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Pneumonia                                       |                  |                  |  |
| subjects affected / exposed                     | 23 / 288 (7.99%) | 12 / 287 (4.18%) |  |
| occurrences causally related to treatment / all | 0 / 27           | 0 / 12           |  |
| deaths causally related to treatment / all      | 0 / 4            | 0 / 3            |  |
| Pneumonia bacterial                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 288 (0.35%)  | 1 / 287 (0.35%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Pneumonia cytomegaloviral                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 288 (0.69%)  | 1 / 287 (0.35%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Pneumonia fungal                                |                  |                  |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 288 (0.35%) | 2 / 287 (0.70%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 2           |  |
| Pneumonia klebsiella                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 2 / 287 (0.70%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Pneumonia pseudomonal                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia respiratory syncytial viral           |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia viral                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Pseudomembranous colitis                        |                 |                 |  |
| subjects affected / exposed                     | 2 / 288 (0.69%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Pseudomonal bacteraemia                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pseudomonal sepsis                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary mycosis                               |                 |                 |  |

|                                                 |                  |                 |  |
|-------------------------------------------------|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 288 (0.35%)  | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pulmonary sepsis                                |                  |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%)  | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pulmonary tuberculosis                          |                  |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%)  | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pyelonephritis                                  |                  |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%)  | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Relapsing fever                                 |                  |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%)  | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Renal graft infection                           |                  |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%)  | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Respiratory tract infection fungal              |                  |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%)  | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| Sepsis                                          |                  |                 |  |
| subjects affected / exposed                     | 10 / 288 (3.47%) | 7 / 287 (2.44%) |  |
| occurrences causally related to treatment / all | 0 / 10           | 0 / 7           |  |
| deaths causally related to treatment / all      | 0 / 4            | 0 / 4           |  |
| Sepsis syndrome                                 |                  |                 |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 288 (0.35%)  | 0 / 287 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Septic shock                                    |                  |                  |  |
| subjects affected / exposed                     | 16 / 288 (5.56%) | 16 / 287 (5.57%) |  |
| occurrences causally related to treatment / all | 0 / 16           | 0 / 16           |  |
| deaths causally related to treatment / all      | 0 / 12           | 0 / 11           |  |
| Sinusitis                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 288 (0.35%)  | 1 / 287 (0.35%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Sinusitis fungal                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 288 (0.00%)  | 1 / 287 (0.35%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Staphylococcal bacteraemia                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 288 (0.35%)  | 0 / 287 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Staphylococcal sepsis                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 288 (0.00%)  | 2 / 287 (0.70%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Subcutaneous abscess                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 288 (0.00%)  | 1 / 287 (0.35%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Systemic candida                                |                  |                  |  |
| subjects affected / exposed                     | 2 / 288 (0.69%)  | 1 / 287 (0.35%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Urinary tract infection                         |                  |                  |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 288 (0.69%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection enterococcal            |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Varicella zoster virus infection                |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Viral upper respiratory tract infection         |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Cachexia                                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dehydration                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diabetes mellitus                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperkalaemia                                   |                 |                 |  |
| subjects affected / exposed                     | 2 / 288 (0.69%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypokalaemia                                    |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 4 / 288 (1.39%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolic acidosis                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 288 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tumour lysis syndrome                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 288 (0.35%) | 0 / 287 (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 %

| <b>Non-serious adverse events</b>                     | Posaconazole (POS)-<br>300 mg | Voriconazole (VOR)-<br>6 mg, 4 mg/200 mg |  |
|-------------------------------------------------------|-------------------------------|------------------------------------------|--|
| Total subjects affected by non-serious adverse events |                               |                                          |  |
| subjects affected / exposed                           | 232 / 288 (80.56%)            | 225 / 287 (78.40%)                       |  |
| Vascular disorders                                    |                               |                                          |  |
| Hypertension                                          |                               |                                          |  |
| subjects affected / exposed                           | 28 / 288 (9.72%)              | 23 / 287 (8.01%)                         |  |
| occurrences (all)                                     | 33                            | 25                                       |  |
| Hypotension                                           |                               |                                          |  |
| subjects affected / exposed                           | 17 / 288 (5.90%)              | 19 / 287 (6.62%)                         |  |
| occurrences (all)                                     | 20                            | 25                                       |  |
| General disorders and administration site conditions  |                               |                                          |  |
| Chest pain                                            |                               |                                          |  |
| subjects affected / exposed                           | 18 / 288 (6.25%)              | 11 / 287 (3.83%)                         |  |
| occurrences (all)                                     | 19                            | 11                                       |  |
| Chills                                                |                               |                                          |  |
| subjects affected / exposed                           | 15 / 288 (5.21%)              | 8 / 287 (2.79%)                          |  |
| occurrences (all)                                     | 19                            | 8                                        |  |
| Fatigue                                               |                               |                                          |  |
| subjects affected / exposed                           | 19 / 288 (6.60%)              | 7 / 287 (2.44%)                          |  |
| occurrences (all)                                     | 20                            | 8                                        |  |
| Oedema peripheral                                     |                               |                                          |  |

|                                                                                          |                          |                          |  |
|------------------------------------------------------------------------------------------|--------------------------|--------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                         | 32 / 288 (11.11%)<br>35  | 24 / 287 (8.36%)<br>27   |  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)                              | 75 / 288 (26.04%)<br>122 | 69 / 287 (24.04%)<br>127 |  |
| Respiratory, thoracic and mediastinal disorders                                          |                          |                          |  |
| Cough<br>subjects affected / exposed<br>occurrences (all)                                | 30 / 288 (10.42%)<br>32  | 24 / 287 (8.36%)<br>24   |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)                             | 27 / 288 (9.38%)<br>28   | 24 / 287 (8.36%)<br>28   |  |
| Epistaxis<br>subjects affected / exposed<br>occurrences (all)                            | 31 / 288 (10.76%)<br>34  | 17 / 287 (5.92%)<br>17   |  |
| Psychiatric disorders                                                                    |                          |                          |  |
| Confusional state<br>subjects affected / exposed<br>occurrences (all)                    | 8 / 288 (2.78%)<br>9     | 16 / 287 (5.57%)<br>16   |  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                             | 18 / 288 (6.25%)<br>19   | 16 / 287 (5.57%)<br>17   |  |
| Investigations                                                                           |                          |                          |  |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)   | 39 / 288 (13.54%)<br>49  | 34 / 287 (11.85%)<br>46  |  |
| Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all) | 36 / 288 (12.50%)<br>46  | 34 / 287 (11.85%)<br>41  |  |
| Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all) | 21 / 288 (7.29%)<br>23   | 28 / 287 (9.76%)<br>33   |  |
| Blood bilirubin increased<br>subjects affected / exposed<br>occurrences (all)            | 24 / 288 (8.33%)<br>38   | 20 / 287 (6.97%)<br>24   |  |
| Blood lactate dehydrogenase                                                              |                          |                          |  |

|                                      |                   |                   |  |
|--------------------------------------|-------------------|-------------------|--|
| increased                            |                   |                   |  |
| subjects affected / exposed          | 13 / 288 (4.51%)  | 17 / 287 (5.92%)  |  |
| occurrences (all)                    | 17                | 20                |  |
| Gamma-glutamyltransferase increased  |                   |                   |  |
| subjects affected / exposed          | 13 / 288 (4.51%)  | 15 / 287 (5.23%)  |  |
| occurrences (all)                    | 15                | 21                |  |
| Platelet count decreased             |                   |                   |  |
| subjects affected / exposed          | 15 / 288 (5.21%)  | 11 / 287 (3.83%)  |  |
| occurrences (all)                    | 21                | 18                |  |
| Cardiac disorders                    |                   |                   |  |
| Tachycardia                          |                   |                   |  |
| subjects affected / exposed          | 11 / 288 (3.82%)  | 18 / 287 (6.27%)  |  |
| occurrences (all)                    | 14                | 23                |  |
| Nervous system disorders             |                   |                   |  |
| Dizziness                            |                   |                   |  |
| subjects affected / exposed          | 21 / 288 (7.29%)  | 12 / 287 (4.18%)  |  |
| occurrences (all)                    | 22                | 12                |  |
| Headache                             |                   |                   |  |
| subjects affected / exposed          | 34 / 288 (11.81%) | 24 / 287 (8.36%)  |  |
| occurrences (all)                    | 45                | 29                |  |
| Blood and lymphatic system disorders |                   |                   |  |
| Anaemia                              |                   |                   |  |
| subjects affected / exposed          | 23 / 288 (7.99%)  | 29 / 287 (10.10%) |  |
| occurrences (all)                    | 41                | 46                |  |
| Febrile neutropenia                  |                   |                   |  |
| subjects affected / exposed          | 21 / 288 (7.29%)  | 18 / 287 (6.27%)  |  |
| occurrences (all)                    | 24                | 22                |  |
| Thrombocytopenia                     |                   |                   |  |
| subjects affected / exposed          | 22 / 288 (7.64%)  | 17 / 287 (5.92%)  |  |
| occurrences (all)                    | 28                | 23                |  |
| Gastrointestinal disorders           |                   |                   |  |
| Abdominal pain                       |                   |                   |  |
| subjects affected / exposed          | 27 / 288 (9.38%)  | 24 / 287 (8.36%)  |  |
| occurrences (all)                    | 31                | 24                |  |
| Constipation                         |                   |                   |  |

|                                                                                                                   |                         |                         |  |
|-------------------------------------------------------------------------------------------------------------------|-------------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                                  | 32 / 288 (11.11%)<br>36 | 23 / 287 (8.01%)<br>26  |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                                                     | 52 / 288 (18.06%)<br>66 | 50 / 287 (17.42%)<br>57 |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                                                        | 65 / 288 (22.57%)<br>83 | 50 / 287 (17.42%)<br>63 |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                                                      | 52 / 288 (18.06%)<br>64 | 38 / 287 (13.24%)<br>57 |  |
| Skin and subcutaneous tissue disorders<br>Rash<br>subjects affected / exposed<br>occurrences (all)                | 19 / 288 (6.60%)<br>22  | 22 / 287 (7.67%)<br>32  |  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 17 / 288 (5.90%)<br>21  | 9 / 287 (3.14%)<br>10   |  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)                                             | 19 / 288 (6.60%)<br>20  | 13 / 287 (4.53%)<br>15  |  |
| Infections and infestations<br>Cytomegalovirus infection<br>subjects affected / exposed<br>occurrences (all)      | 15 / 288 (5.21%)<br>17  | 14 / 287 (4.88%)<br>16  |  |
| Pneumonia<br>subjects affected / exposed<br>occurrences (all)                                                     | 14 / 288 (4.86%)<br>14  | 15 / 287 (5.23%)<br>15  |  |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all)      | 25 / 288 (8.68%)<br>25  | 14 / 287 (4.88%)<br>15  |  |
| Hypocalcaemia<br>subjects affected / exposed<br>occurrences (all)                                                 | 15 / 288 (5.21%)<br>25  | 13 / 287 (4.53%)<br>27  |  |

|                             |                   |                   |  |
|-----------------------------|-------------------|-------------------|--|
| Hypokalaemia                |                   |                   |  |
| subjects affected / exposed | 78 / 288 (27.08%) | 49 / 287 (17.07%) |  |
| occurrences (all)           | 133               | 72                |  |
| Hypomagnesaemia             |                   |                   |  |
| subjects affected / exposed | 29 / 288 (10.07%) | 18 / 287 (6.27%)  |  |
| occurrences (all)           | 48                | 20                |  |
| Hyponatraemia               |                   |                   |  |
| subjects affected / exposed | 12 / 288 (4.17%)  | 19 / 287 (6.62%)  |  |
| occurrences (all)           | 19                | 26                |  |
| Hypophosphataemia           |                   |                   |  |
| subjects affected / exposed | 22 / 288 (7.64%)  | 9 / 287 (3.14%)   |  |
| occurrences (all)           | 24                | 11                |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                                                                                                    |
|------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 14 December 2012 | Amendment 01: Primary reason for amendment was to clarify and simplify the study drug dosing by treatment arms in regard to the dosing for intravenous (IV) and oral posaconazole and voriconazole.                                                                                                                                                          |
| 01 July 2013     | Amendment 02: Primary reason for amendment was to exclude participants <18 years of age.                                                                                                                                                                                                                                                                     |
| 14 January 2015  | Amendment 03: Primary reason for amendment was to allow the enrollment of adolescents outside of the EU (ie, in those regions with an approved indication for use of oral POS in the adolescent age population ( $\geq 13$ years of age)).                                                                                                                   |
| 12 August 2016   | Amendment 04: Primary reason for amendment was to change the primary study objective and endpoint of global clinical response at Week 6 (FAS population) to a key secondary study objective and endpoint. The all-cause mortality at Week 6 (ITT population) secondary objective and study endpoint was changed to the primary objective and study endpoint. |
| 22 February 2019 | Amendment 05: Primary reason for amendment was to clarify protocol and statistical analyses, including approximate sample size and power calculation, time windows used for assessment, and the elimination of 2 secondary objectives for which data analyses was no longer planned.                                                                         |

Notes:

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported