



## Clinical trial results:

### A Phase 1/2 Study of ARQ 092 (Miransertib) in Subjects with PIK3CA-related Overgrowth Spectrum and Proteus Syndrome

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2016-000558-37 |
| Trial protocol           | IT FR ES GB DE |
| Global end of trial date | 11 April 2022  |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 11 October 2022 |
| First version publication date | 11 October 2022 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 7075-002 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |                                    |
|------------------------------------|------------------------------------|
| ISRCTN number                      | -                                  |
| ClinicalTrials.gov id (NCT number) | NCT03094832                        |
| WHO universal trial number (UTN)   | -                                  |
| Other trial identifiers            | Merck Protocol Number: MK-7075-002 |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Merck Sharp & Dohme LLC  |
| Sponsor organisation address | 126 East Lincoln Avenue, P.O. Box 2000, Rahway, NJ, United States, 07065                   |
| Public contact               | Clinical Trials Disclosure, Merck Sharp & Dohme LLC,<br>ClinicalTrialsDisclosure@merck.com |
| Scientific contact           | Clinical Trials Disclosure, Merck Sharp & Dohme LLC,<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                       | 11 April 2022 |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 11 April 2022 |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 11 April 2022 |
| Was the trial ended prematurely?                     | Yes           |

Notes:

## General information about the trial

Main objective of the trial:

In this study, oral miransertib (MK-7075, formerly called ARQ 092) was administered to participants at least 2 years of age with phosphatidylinositol-4,5-bisphosphate 3 kinase, catalytic subunit alpha (PIK3CA)-related Overgrowth Spectrum (PROS) and Proteus Syndrome (PS) (MOSAIC). The study consists of two parts: Part A and Part B. In Part A, participants with either PROS or PS received miransertib orally once daily (QD) for first 3 cycles (each cycle length=28 days) with an option to increase the dose at the investigator's discretion. Part A was closed to enrollment under Amendment 6. In Part B Cohorts 1, 2, and 3 participants received a starting dose of miransertib QD for the first 3 cycles and then the dose was increased at the investigator's discretion, provided no clinically significant drug related toxicity was observed. In Part B Cohort 4 participants previously treated with miransertib or currently receiving miransertib were enrolled under Compassionate Use/Expanded Access.

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                          | 16 May 2017 |
| 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 | Australia: 1      |
| Country: Number of subjects enrolled | Italy: 13         |
| Country: Number of subjects enrolled | United States: 36 |
| Worldwide total number of subjects   | 50                |
| EEA total number of subjects         | 13                |

Notes:

### Subjects enrolled per age group

|   |   |
|---|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days)                      | 0 |
| Infants and toddlers (28 days-23          | 0 |

|                           |    |
|---------------------------|----|
| months)                   |    |
| Children (2-11 years)     | 29 |
| Adolescents (12-17 years) | 13 |
| Adults (18-64 years)      | 8  |
| From 65 to 84 years       | 0  |
| 85 years and over         | 0  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

50 participants were enrolled in the study of which 49 participants received at least one dose of treatment and was used for safety analysis.

### Period 1

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

### Arms

|                              |                             |
|------------------------------|-----------------------------|
| Are arms mutually exclusive? | Yes                         |
| <b>Arm title</b>             | Part A: Miransertib PROS/PS |

Arm description:

During Cycles 1-3, participants with either PROS (phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha [PIK3CA]-related Overgrowth Spectrum) or PS (Proteus syndrome) received miransertib 15 mg/m<sup>2</sup> once daily (QD) (each cycle length = 28 days). From Cycles 4-48 or until disease progression, unacceptable toxicity, or discontinuation, participants received miransertib dose titrated to 25 mg/m<sup>2</sup> and then titrated to 35 mg/m<sup>2</sup> orally QD at the investigator's discretion.

|  |                  |
|--|------------------|
| Arm type                               | Experimental     |
| Investigational medicinal product name | Miransertib      |
| Investigational medicinal product code |                  |
| Other name                             | MK-7075, ARQ 092 |
| Pharmaceutical forms                   | Capsule          |
| Routes of administration               | Oral use         |

Dosage and administration details:

Initial dose of 15 mg/m<sup>2</sup> or 25 mg/m<sup>2</sup> orally QD and then titrated up to 25 mg/m<sup>2</sup> or 35 mg/m<sup>2</sup> orally QD at the investigator's discretion.

|                  |                                     |
|------------------|-------------------------------------|
| <b>Arm title</b> | Part B: Miransertib PROS (Cohort 1) |
|------------------|-------------------------------------|

Arm description:

During Cycles 1-3, participants with PROS who have a measurable lesion by volumetric magnetic resonance imaging (MRI) received miransertib 15 mg/m<sup>2</sup> QD (each cycle length = 28 days). From cycles 4-48 or until disease progression, unacceptable toxicity, or discontinuation, participants received miransertib dose titrated to 25 mg/m<sup>2</sup> orally QD at the investigator's discretion.

|  |                  |
|--|------------------|
| Arm type                               | Experimental     |
| Investigational medicinal product name | Miransertib      |
| Investigational medicinal product code |                  |
| Other name                             | MK-7075, ARQ 092 |
| Pharmaceutical forms                   | Capsule          |
| Routes of administration               | Oral use         |

Dosage and administration details:

Initial dose of 15 mg/m<sup>2</sup> or 25 mg/m<sup>2</sup> orally QD and then titrated up to 25 mg/m<sup>2</sup> or 35 mg/m<sup>2</sup> orally QD at the investigator's discretion.

|                  |                                   |
|------------------|-----------------------------------|
| <b>Arm title</b> | Part B: Miransertib PS (Cohort 2) |
|------------------|-----------------------------------|

Arm description:

During Cycles 1-3, participants with PS who have a measurable lesion by standardized digital photography received miransertib 15 mg/m<sup>2</sup> QD (each cycle length = 28 days). From cycles 4-48 or until disease progression, unacceptable toxicity, or discontinuation, participants received miransertib dose titrated to 25 mg/m<sup>2</sup> orally QD at the investigator's discretion.

|  |                  |
|--|------------------|
| Arm type                               | Experimental     |
| Investigational medicinal product name | Miransertib      |
| Investigational medicinal product code |                  |
| Other name                             | MK-7075, ARQ 092 |
| Pharmaceutical forms                   | Capsule          |
| Routes of administration               | Oral use         |

Dosage and administration details:

Initial dose of 15 mg/m<sup>2</sup> or 25 mg/m<sup>2</sup> orally QD and then titrated up to 25 mg/m<sup>2</sup> or 35 mg/m<sup>2</sup> orally QD at the investigator's discretion.

|                  |  |
|------------------|--|
| <b>Arm title</b> | Part B: Miransertib PROS/PS (Cohort 3) |
|------------------|--|

Arm description:

During Cycles 1-3, participants with PROS or PS who do not meet all the eligibility criteria for Cohorts 1 or 2 received miransertib 15 mg/m<sup>2</sup> QD (each cycle length = 28 days). From cycles 4-48 or until disease progression, unacceptable toxicity, or discontinuation, participants received miransertib dose titrated to 25 mg/m<sup>2</sup> orally QD at the investigator's discretion.

|  |                  |
|--|------------------|
| Arm type                               | Experimental     |
| Investigational medicinal product name | Miransertib      |
| Investigational medicinal product code |                  |
| Other name                             | MK-7075, ARQ 092 |
| Pharmaceutical forms                   | Capsule          |
| Routes of administration               | Oral use         |

Dosage and administration details:

Initial dose of 15 mg/m<sup>2</sup> or 25 mg/m<sup>2</sup> orally QD and then titrated up to 25 mg/m<sup>2</sup> or 35 mg/m<sup>2</sup> orally QD at the investigator's discretion.

|                  |  |
|------------------|--|
| <b>Arm title</b> | Part B: Miransertib Compassionate Use/Expanded Access (Cohort 4) |
|------------------|--|

Arm description:

During cycles 1-48 (each cycle length = 28 days) or until disease progression, unacceptable toxicity, or discontinuation, participants previously treated with miransertib or currently receiving miransertib under Compassionate Use/Expanded Access continued to receive the current dose of miransertib (did not exceed 25 mg/m<sup>2</sup>).

|  |                  |
|--|------------------|
| Arm type                               | Experimental     |
| Investigational medicinal product name | Miransertib      |
| Investigational medicinal product code |                  |
| Other name                             | MK-7075, ARQ 092 |
| Pharmaceutical forms                   | Capsule          |
| Routes of administration               | Oral use         |

Dosage and administration details:

Initial dose of 15 mg/m<sup>2</sup> or 25 mg/m<sup>2</sup> orally QD and then titrated up to 25 mg/m<sup>2</sup> or 35 mg/m<sup>2</sup> orally QD at the investigator's discretion.

| <b>Number of subjects in period 1</b> | Part A: Miransertib PROS/PS | Part B: Miransertib PROS (Cohort 1) | Part B: Miransertib PS (Cohort 2) |
|---------------------------------------|-----------------------------|-------------------------------------|-----------------------------------|
| Started                               | 17                          | 22                                  | 1                                 |
| Treated                               | 17                          | 22                                  | 1                                 |
| Completed                             | 2                           | 2                                   | 0                                 |
| Not completed                         | 15                          | 20                                  | 1                                 |
| Other                                 | 13                          | 20                                  | 1                                 |
| Death                                 | 1                           | -                                   | -                                 |
| Withdrawal by Parent/Guardian         | 1                           | -                                   | -                                 |

|                   |   |   |   |
|-------------------|---|---|---|
| Lost to follow-up | - | - | - |
|-------------------|---|---|---|

| Number of subjects in period 1 | Part B: Miransertib<br>PROS/PS (Cohort 3) | Part B:Miransertib<br>Compassionate<br>Use/Expanded<br>Access(Cohort 4) |
|--------------------------------|---|---|
|                                |   |   |
| Started                        | 8   | 2   |
| Treated                        | 8   | 1   |
| Completed                      | 0   | 0   |
| Not completed                  | 8   | 2   |
| Other                          | 7   | 1   |
| Death                          | -   | -   |
| Withdrawal by Parent/Guardian  | -   | -   |
| Lost to follow-up              | 1   | 1   |

## Baseline characteristics

### Reporting groups

|   |  |
|---|--|
| Reporting group title   | Part A: Miransertib PROS/PS                                      |
| Reporting group description:  |  |
| During Cycles 1-3, participants with either PROS (phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha [PIK3CA]-related Overgrowth Spectrum) or PS (Proteus syndrome) received miransertib 15 mg/m <sup>2</sup> once daily (QD) (each cycle length = 28 days). From Cycles 4-48 or until disease progression, unacceptable toxicity, or discontinuation, participants received miransertib dose titrated to 25 mg/m <sup>2</sup> and then titrated to 35 mg/m <sup>2</sup> orally QD at the investigator's discretion. |  |
| Reporting group title   | Part B: Miransertib PROS (Cohort 1)                              |
| Reporting group description:  |  |
| During Cycles 1-3, participants with PROS who have a measurable lesion by volumetric magnetic resonance imaging (MRI) received miransertib 15 mg/m <sup>2</sup> QD (each cycle length = 28 days). From cycles 4-48 or until disease progression, unacceptable toxicity, or discontinuation, participants received miransertib dose titrated to 25 mg/m <sup>2</sup> orally QD at the investigator's discretion.   |  |
| Reporting group title   | Part B: Miransertib PS (Cohort 2)                                |
| Reporting group description:  |  |
| During Cycles 1-3, participants with PS who have a measurable lesion by standardized digital photography received miransertib 15 mg/m <sup>2</sup> QD (each cycle length = 28 days). From cycles 4-48 or until disease progression, unacceptable toxicity, or discontinuation, participants received miransertib dose titrated to 25 mg/m <sup>2</sup> orally QD at the investigator's discretion.  |  |
| Reporting group title   | Part B: Miransertib PROS/PS (Cohort 3)                           |
| Reporting group description:  |  |
| During Cycles 1-3, participants with PROS or PS who do not meet all the eligibility criteria for Cohorts 1 or 2 received miransertib 15 mg/m <sup>2</sup> QD (each cycle length = 28 days). From cycles 4-48 or until disease progression, unacceptable toxicity, or discontinuation, participants received miransertib dose titrated to 25 mg/m <sup>2</sup> orally QD at the investigator's discretion.   |  |
| Reporting group title   | Part B: Miransertib Compassionate Use/Expanded Access (Cohort 4) |
| Reporting group description:  |  |
| During cycles 1-48 (each cycle length = 28 days) or until disease progression, unacceptable toxicity, or discontinuation, participants previously treated with miransertib or currently receiving miransertib under Compassionate Use/Expanded Access continued to receive the current dose of miransertib (did not exceed 25 mg/m <sup>2</sup> ).  |  |

| Reporting group values  | Part A: Miransertib PROS/PS | Part B: Miransertib PROS (Cohort 1) | Part B: Miransertib PS (Cohort 2) |
|---|-----------------------------|-------------------------------------|-----------------------------------|
| Number of subjects  | 17                          | 22                                  | 1                                 |
| Age Categorical   |                             |                                     |                                   |
| Units: Participants   |                             |                                     |                                   |
| In utero  |                             |                                     |                                   |
| Preterm newborn infants (gestational age < 37 wks)                                      |                             |                                     |                                   |
| Newborns (0-27 days)  |                             |                                     |                                   |
| Infants and toddlers (28 days-23 months)  |                             |                                     |                                   |
| Children (2-11 years)   |                             |                                     |                                   |
| Adolescents (12-17 years)   |                             |                                     |                                   |
| Adults (18-64 years)  |                             |                                     |                                   |
| From 65-84 years  |                             |                                     |                                   |
| 85 years and over   |                             |                                     |                                   |
| Age Continuous  |                             |                                     |                                   |
| Standard deviation was not calculatable when n<2 for Part B Miransertib PS Cohort 2 arm |                             |                                     |                                   |
| Units: years  |                             |                                     |                                   |

|                    |       |       |        |
|--------------------|-------|-------|--------|
| arithmetic mean    | 8.2   | 9.9   | 12.0   |
| standard deviation | ± 9.9 | ± 6.7 | ± 9999 |

|   |    |    |   |
|---|----|----|---|
| Gender Categorical<br>Units: Participants |    |    |   |
| Female                                    | 9  | 10 | 0 |
| Male                                      | 8  | 12 | 1 |
| Race<br>Units: Subjects                   |    |    |   |
| American Indian or Alaska Native          | 0  | 0  | 0 |
| Asian                                     | 0  | 3  | 0 |
| Native Hawaiian or Other Pacific Islander | 0  | 0  | 0 |
| Black or African American                 | 0  | 5  | 0 |
| White                                     | 17 | 13 | 1 |
| More than one race                        | 0  | 1  | 0 |
| Unknown or Not Reported                   | 0  | 0  | 0 |
| Ethnicity<br>Units: Subjects              |    |    |   |
| Hispanic Or Latino                        | 2  | 1  | 0 |
| Not Hispanic Or Latino                    | 15 | 20 | 1 |
| Not Reported                              | 0  | 1  | 0 |

| Reporting group values  | Part B: Miransertib PROS/PS (Cohort 3) | Part B: Miransertib Compassionate Use/Expanded Access (Cohort 4) | Total |
|---|--|--|-------|
| Number of subjects  | 8                                      | 2  | 50    |
| Age Categorical<br>Units: Participants  |  |  |       |
| In utero  |  |  |       |
| Preterm newborn infants (gestational age < 37 wks)                                      |  |  |       |
| Newborns (0-27 days)  |  |  |       |
| Infants and toddlers (28 days-23 months)  |  |  |       |
| Children (2-11 years)   |  |  |       |
| Adolescents (12-17 years)   |  |  |       |
| Adults (18-64 years)  |  |  |       |
| From 65-84 years  |  |  |       |
| 85 years and over   |  |  |       |
| Age Continuous  |  |  |       |
| Standard deviation was not calculatable when n<2 for Part B Miransertib PS Cohort 2 arm |  |  |       |
| Units: years  |  |  |       |
| arithmetic mean   | 12.5                                   | 20.0   |       |
| standard deviation  | ± 9.1                                  | ± 1.4  | -     |
| Gender Categorical<br>Units: Participants   |  |  |       |
| Female  | 3                                      | 1  | 23    |
| Male  | 5                                      | 1  | 27    |
| Race<br>Units: Subjects   |  |  |       |
| American Indian or Alaska Native  | 0                                      | 0  | 0     |



|   |   |   |    |
|---|---|---|----|
| Asian                                     | 1 | 0 | 4  |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0  |
| Black or African American                 | 1 | 0 | 6  |
| White                                     | 6 | 2 | 39 |
| More than one race                        | 0 | 0 | 1  |
| Unknown or Not Reported                   | 0 | 0 | 0  |
| Ethnicity                                 |   |   |    |
| Units: Subjects                           |   |   |    |
| Hispanic Or Latino                        | 0 | 0 | 3  |
| Not Hispanic Or Latino                    | 8 | 2 | 46 |
| Not Reported                              | 0 | 0 | 1  |

## End points

### End points reporting groups

|   |  |
|---|--|
| Reporting group title   | Part A: Miransertib PROS/PS                                      |
| Reporting group description:<br>During Cycles 1-3, participants with either PROS (phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha [PIK3CA]-related Overgrowth Spectrum) or PS (Proteus syndrome) received miransertib 15 mg/m <sup>2</sup> once daily (QD) (each cycle length = 28 days). From Cycles 4-48 or until disease progression, unacceptable toxicity, or discontinuation, participants received miransertib dose titrated to 25 mg/m <sup>2</sup> and then titrated to 35 mg/m <sup>2</sup> orally QD at the investigator's discretion. |  |
| Reporting group title   | Part B: Miransertib PROS (Cohort 1)                              |
| Reporting group description:<br>During Cycles 1-3, participants with PROS who have a measurable lesion by volumetric magnetic resonance imaging (MRI) received miransertib 15 mg/m <sup>2</sup> QD (each cycle length = 28 days). From cycles 4-48 or until disease progression, unacceptable toxicity, or discontinuation, participants received miransertib dose titrated to 25 mg/m <sup>2</sup> orally QD at the investigator's discretion.   |  |
| Reporting group title   | Part B: Miransertib PS (Cohort 2)                                |
| Reporting group description:<br>During Cycles 1-3, participants with PS who have a measurable lesion by standardized digital photography received miransertib 15 mg/m <sup>2</sup> QD (each cycle length = 28 days). From cycles 4-48 or until disease progression, unacceptable toxicity, or discontinuation, participants received miransertib dose titrated to 25 mg/m <sup>2</sup> orally QD at the investigator's discretion.  |  |
| Reporting group title   | Part B: Miransertib PROS/PS (Cohort 3)                           |
| Reporting group description:<br>During Cycles 1-3, participants with PROS or PS who do not meet all the eligibility criteria for Cohorts 1 or 2 received miransertib 15 mg/m <sup>2</sup> QD (each cycle length = 28 days). From cycles 4-48 or until disease progression, unacceptable toxicity, or discontinuation, participants received miransertib dose titrated to 25 mg/m <sup>2</sup> orally QD at the investigator's discretion.   |  |
| Reporting group title   | Part B: Miransertib Compassionate Use/Expanded Access (Cohort 4) |
| Reporting group description:<br>During cycles 1-48 (each cycle length = 28 days) or until disease progression, unacceptable toxicity, or discontinuation, participants previously treated with miransertib or currently receiving miransertib under Compassionate Use/Expanded Access continued to receive the current dose of miransertib (did not exceed 25 mg/m <sup>2</sup> ).  |  |

### Primary: Number of Participants Who Experienced an Adverse Event (AE)

|   |   |
|---|---|
| End point title   | Number of Participants Who Experienced an Adverse Event (AE) <sup>[1]</sup> |
| End point description:<br>An AE was defined as any untoward medical occurrence associated with the use of a drug in a participant, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product and does not imply any judgment about causality. The analysis population included all participants who have received at least one dose of study treatment. |   |
| End point type  | Primary   |
| End point timeframe:<br>Up to approximately 48 months   |   |
| Notes:<br>[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.<br>Justification: There was no statistical analysis planned for this endpoint.  |   |

| End point values            | Part A:<br>Miransertib<br>PROS/PS | Part B:<br>Miransertib<br>PROS (Cohort<br>1) | Part B:<br>Miransertib PS<br>(Cohort 2) | Part B:<br>Miransertib<br>PROS/PS<br>(Cohort 3) |
|-----------------------------|-----------------------------------|--|---|---|
| Subject group type          | Reporting group                   | Reporting group                              | Reporting group                         | Reporting group                                 |
| Number of subjects analysed | 17                                | 22   | 1                                       | 8   |
| Units: Participants         | 17                                | 20   | 0                                       | 6   |

| End point values            | Part<br>B:Miransertib<br>Compassionate<br>Use/Expanded<br>Access(Cohort<br>4) |  |  |  |
|-----------------------------|---|--|--|--|
| Subject group type          | Reporting group   |  |  |  |
| Number of subjects analysed | 1   |  |  |  |
| Units: Participants         | 1   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Participants Who Discontinued Study Treatment Due to an AE

|                 |   |
|-----------------|---|
| End point title | Number of Participants Who Discontinued Study Treatment Due to an AE <sup>[2]</sup> |
|-----------------|---|

End point description:

An AE was defined as any untoward medical occurrence associated with the use of a drug in a participant, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product and does not imply any judgment about causality. The analysis population included all participants who have received at least one dose of study treatment.

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

End point timeframe:

Up to approximately 45 months

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There was no statistical analysis planned for this endpoint.

| End point values            | Part A:<br>Miransertib<br>PROS/PS | Part B:<br>Miransertib<br>PROS (Cohort<br>1) | Part B:<br>Miransertib PS<br>(Cohort 2) | Part B:<br>Miransertib<br>PROS/PS<br>(Cohort 3) |
|-----------------------------|-----------------------------------|--|---|---|
| Subject group type          | Reporting group                   | Reporting group                              | Reporting group                         | Reporting group                                 |
| Number of subjects analysed | 17                                | 22   | 1                                       | 8   |
| Units: Participants         | 2                                 | 0  | 0                                       | 0   |

| End point values | Part B: |  |  |  |
|------------------|---------|--|--|--|
|------------------|---------|--|--|--|

|                             |   |  |  |  |
|-----------------------------|---|--|--|--|
|                             | Miransertib<br>Compassionate<br>Use/Expanded<br>Access(Cohort<br>4) |  |  |  |
| Subject group type          | Reporting group   |  |  |  |
| Number of subjects analysed | 1   |  |  |  |
| Units: Participants         | 0   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to approximately 48 months

Adverse event reporting additional description:

All cause mortality was reported on all enrolled participants and non-serious and serious AEs were reported on all participants who received at least one dose of study treatment. Per protocol, disease progression (DP) was not considered an AE unless related to treatment.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 24.1 |
|--------------------|------|

### Reporting groups

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Part A: Miransertib PROS/PS |
|-----------------------|-----------------------------|

Reporting group description:

During Cycles 1-3, participants with either PROS (phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha [PIK3CA]-related Overgrowth Spectrum) or PS (Proteus syndrome) received miransertib 15 mg/m<sup>2</sup> once daily (QD) (each cycle length = 28 days). From Cycles 4-48 or until disease progression, unacceptable toxicity, or discontinuation, participants received miransertib dose titrated to 25 mg/m<sup>2</sup> and then titrated to 35 mg/m<sup>2</sup> orally QD at the investigator's discretion.

|                       |                                     |
|-----------------------|-------------------------------------|
| Reporting group title | Part B: Miransertib PROS (Cohort 1) |
|-----------------------|-------------------------------------|

Reporting group description:

During Cycles 1-3, participants with PROS who have a measurable lesion by volumetric magnetic resonance imaging (MRI) received miransertib 15 mg/m<sup>2</sup> QD (each cycle length = 28 days). From cycles 4-48 or until disease progression, unacceptable toxicity, or discontinuation, participants received miransertib dose titrated to 25 mg/m<sup>2</sup> orally QD at the investigator's discretion.

|                       |                                   |
|-----------------------|-----------------------------------|
| Reporting group title | Part B: Miransertib PS (Cohort 2) |
|-----------------------|-----------------------------------|

Reporting group description:

During Cycles 1-3, participants with PS who have a measurable lesion by standardized digital photography received miransertib 15 mg/m<sup>2</sup> QD (each cycle length = 28 days). From cycles 4-48 or until disease progression, unacceptable toxicity, or discontinuation, participants received miransertib dose titrated to 25 mg/m<sup>2</sup> orally QD at the investigator's discretion.

|                       |  |
|-----------------------|--|
| Reporting group title | Part B: Miransertib PROS/PS (Cohort 3) |
|-----------------------|--|

Reporting group description:

During Cycles 1-3, participants with PROS or PS who do not meet all the eligibility criteria for Cohorts 1 or 2 received miransertib 15 mg/m<sup>2</sup> QD (each cycle length = 28 days). From cycles 4-48 or until disease progression, unacceptable toxicity, or discontinuation, participants received miransertib dose titrated to 25 mg/m<sup>2</sup> orally QD at the investigator's discretion.

|                       |  |
|-----------------------|--|
| Reporting group title | Part B: Miransertib Compassionate Use/Expanded Access (Cohort 4) |
|-----------------------|--|

Reporting group description:

During cycles 1-48 (each cycle length = 28 days) or until disease progression, unacceptable toxicity, or discontinuation, participants previously treated with miransertib or currently receiving miransertib under Compassionate Use/Expanded Access continued to receive the current dose of miransertib (did not exceed 25 mg/m<sup>2</sup>).

| Serious adverse events                            | Part A: Miransertib PROS/PS | Part B: Miransertib PROS (Cohort 1) | Part B: Miransertib PS (Cohort 2) |
|---|-----------------------------|-------------------------------------|-----------------------------------|
| Total subjects affected by serious adverse events |                             |                                     |                                   |
| subjects affected / exposed                       | 4 / 17 (23.53%)             | 3 / 22 (13.64%)                     | 0 / 1 (0.00%)                     |
| number of deaths (all causes)                     | 1                           | 0                                   | 0                                 |
| number of deaths resulting from                   | 0                           | 0                                   | 0                                 |

|   |                |                |               |
|---|----------------|----------------|---------------|
| adverse events                                  |                |                |               |
| Nervous system disorders                        |                |                |               |
| Febrile convulsion                              |                |                |               |
| subjects affected / exposed                     | 1 / 17 (5.88%) | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Blood and lymphatic system disorders            |                |                |               |
| Anaemia   |                |                |               |
| subjects affected / exposed                     | 1 / 17 (5.88%) | 1 / 22 (4.55%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Gastrointestinal disorders                      |                |                |               |
| Diarrhoea                                       |                |                |               |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Mouth haemorrhage                               |                |                |               |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Nausea  |                |                |               |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Vomiting  |                |                |               |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Infections and infestations                     |                |                |               |
| Cellulitis                                      |                |                |               |
| subjects affected / exposed                     | 1 / 17 (5.88%) | 2 / 22 (9.09%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 3          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Metabolism and nutrition disorders              |                |                |               |
| Dehydration                                     |                |                |               |

|   |                |                |               |
|---|----------------|----------------|---------------|
| subjects affected / exposed                     | 1 / 17 (5.88%) | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0         |

| <b>Serious adverse events</b>                     | Part B: Miransertib<br>PROS/PS (Cohort 3) | Part B: Miransertib<br>Compassionate<br>Use/Expanded<br>Access (Cohort 4) |  |
|---|---|---|--|
| Total subjects affected by serious adverse events |   |   |  |
| subjects affected / exposed                       | 1 / 8 (12.50%)                            | 0 / 1 (0.00%)   |  |
| number of deaths (all causes)                     | 0   | 0   |  |
| number of deaths resulting from adverse events    | 0   | 0   |  |
| Nervous system disorders                          |   |   |  |
| Febrile convulsion                                |   |   |  |
| subjects affected / exposed                       | 0 / 8 (0.00%)                             | 0 / 1 (0.00%)   |  |
| occurrences causally related to treatment / all   | 0 / 0                                     | 0 / 0   |  |
| deaths causally related to treatment / all        | 0 / 0                                     | 0 / 0   |  |
| Blood and lymphatic system disorders              |   |   |  |
| Anaemia   |   |   |  |
| subjects affected / exposed                       | 0 / 8 (0.00%)                             | 0 / 1 (0.00%)   |  |
| occurrences causally related to treatment / all   | 0 / 0                                     | 0 / 0   |  |
| deaths causally related to treatment / all        | 0 / 0                                     | 0 / 0   |  |
| Gastrointestinal disorders                        |   |   |  |
| Diarrhoea   |   |   |  |
| subjects affected / exposed                       | 1 / 8 (12.50%)                            | 0 / 1 (0.00%)   |  |
| occurrences causally related to treatment / all   | 0 / 1                                     | 0 / 0   |  |
| deaths causally related to treatment / all        | 0 / 0                                     | 0 / 0   |  |
| Mouth haemorrhage                                 |   |   |  |
| subjects affected / exposed                       | 1 / 8 (12.50%)                            | 0 / 1 (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                       | 1 / 8 (12.50%)                            | 0 / 1 (0.00%)   |  |
| occurrences causally related to treatment / all   | 0 / 1                                     | 0 / 0   |  |
| deaths causally related to treatment / all        | 0 / 0                                     | 0 / 0   |  |
| Vomiting  |   |   |  |

|   |                |               |  |
|---|----------------|---------------|--|
| subjects affected / exposed                     | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| <b>Infections and infestations</b>              |                |               |  |
| Cellulitis                                      |                |               |  |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| <b>Metabolism and nutrition disorders</b>       |                |               |  |
| Dehydration                                     |                |               |  |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 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>  | Part A: Miransertib<br>PROS/PS | Part B: Miransertib<br>PROS (Cohort 1) | Part B: Miransertib<br>PS (Cohort 2) |
|--|--------------------------------|--|--------------------------------------|
| Total subjects affected by non-serious adverse events                      |                                |  |                                      |
| subjects affected / exposed  | 17 / 17 (100.00%)              | 18 / 22 (81.82%)                       | 0 / 1 (0.00%)                        |
| <b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b> |                                |  |                                      |
| Haemangioma  |                                |  |                                      |
| subjects affected / exposed  | 1 / 17 (5.88%)                 | 0 / 22 (0.00%)                         | 0 / 1 (0.00%)                        |
| occurrences (all)  | 1                              | 0                                      | 0                                    |
| <b>Vascular disorders</b>  |                                |  |                                      |
| Deep vein thrombosis   |                                |  |                                      |
| subjects affected / exposed  | 0 / 17 (0.00%)                 | 0 / 22 (0.00%)                         | 0 / 1 (0.00%)                        |
| occurrences (all)  | 0                              | 0                                      | 0                                    |
| Hypertension   |                                |  |                                      |
| subjects affected / exposed  | 1 / 17 (5.88%)                 | 0 / 22 (0.00%)                         | 0 / 1 (0.00%)                        |
| occurrences (all)  | 1                              | 0                                      | 0                                    |
| Hypotension  |                                |  |                                      |
| subjects affected / exposed  | 0 / 17 (0.00%)                 | 0 / 22 (0.00%)                         | 0 / 1 (0.00%)                        |
| occurrences (all)  | 0                              | 0                                      | 0                                    |
| Venous haemorrhage   |                                |  |                                      |



|  |                 |                 |               |
|--|-----------------|-----------------|---------------|
| subjects affected / exposed                          | 0 / 17 (0.00%)  | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)                                    | 0               | 0               | 0             |
| Lymphorrhoea   |                 |                 |               |
| subjects affected / exposed                          | 0 / 17 (0.00%)  | 1 / 22 (4.55%)  | 0 / 1 (0.00%) |
| occurrences (all)                                    | 0               | 2               | 0             |
| General disorders and administration site conditions |                 |                 |               |
| Chest pain   |                 |                 |               |
| subjects affected / exposed                          | 1 / 17 (5.88%)  | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)                                    | 1               | 0               | 0             |
| Asthenia   |                 |                 |               |
| subjects affected / exposed                          | 1 / 17 (5.88%)  | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)                                    | 1               | 0               | 0             |
| Chills   |                 |                 |               |
| subjects affected / exposed                          | 0 / 17 (0.00%)  | 1 / 22 (4.55%)  | 0 / 1 (0.00%) |
| occurrences (all)                                    | 0               | 1               | 0             |
| Face oedema  |                 |                 |               |
| subjects affected / exposed                          | 0 / 17 (0.00%)  | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)                                    | 0               | 0               | 0             |
| Fatigue  |                 |                 |               |
| subjects affected / exposed                          | 2 / 17 (11.76%) | 3 / 22 (13.64%) | 0 / 1 (0.00%) |
| occurrences (all)                                    | 7               | 4               | 0             |
| Inflammation   |                 |                 |               |
| subjects affected / exposed                          | 1 / 17 (5.88%)  | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)                                    | 1               | 0               | 0             |
| Influenza like illness                               |                 |                 |               |
| subjects affected / exposed                          | 2 / 17 (11.76%) | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)                                    | 2               | 0               | 0             |
| Lithiasis  |                 |                 |               |
| subjects affected / exposed                          | 1 / 17 (5.88%)  | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)                                    | 1               | 0               | 0             |
| Localised oedema                                     |                 |                 |               |
| subjects affected / exposed                          | 0 / 17 (0.00%)  | 1 / 22 (4.55%)  | 0 / 1 (0.00%) |
| occurrences (all)                                    | 0               | 1               | 0             |
| Mucosal inflammation                                 |                 |                 |               |

|  |                  |                 |               |
|--|------------------|-----------------|---------------|
| subjects affected / exposed              | 3 / 17 (17.65%)  | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)                        | 4                | 0               | 0             |
| Non-cardiac chest pain                   |                  |                 |               |
| subjects affected / exposed              | 0 / 17 (0.00%)   | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)                        | 0                | 0               | 0             |
| Oedema peripheral                        |                  |                 |               |
| subjects affected / exposed              | 1 / 17 (5.88%)   | 1 / 22 (4.55%)  | 0 / 1 (0.00%) |
| occurrences (all)                        | 1                | 1               | 0             |
| Pain                                     |                  |                 |               |
| subjects affected / exposed              | 0 / 17 (0.00%)   | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)                        | 0                | 0               | 0             |
| Pyrexia                                  |                  |                 |               |
| subjects affected / exposed              | 15 / 17 (88.24%) | 3 / 22 (13.64%) | 0 / 1 (0.00%) |
| occurrences (all)                        | 74               | 3               | 0             |
| Suprapubic pain                          |                  |                 |               |
| subjects affected / exposed              | 1 / 17 (5.88%)   | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)                        | 2                | 0               | 0             |
| Swelling                                 |                  |                 |               |
| subjects affected / exposed              | 1 / 17 (5.88%)   | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)                        | 1                | 0               | 0             |
| Thirst                                   |                  |                 |               |
| subjects affected / exposed              | 0 / 17 (0.00%)   | 2 / 22 (9.09%)  | 0 / 1 (0.00%) |
| occurrences (all)                        | 0                | 2               | 0             |
| Reproductive system and breast disorders |                  |                 |               |
| Oedema genital                           |                  |                 |               |
| subjects affected / exposed              | 1 / 17 (5.88%)   | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)                        | 1                | 0               | 0             |
| Perineal erythema                        |                  |                 |               |
| subjects affected / exposed              | 1 / 17 (5.88%)   | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)                        | 1                | 0               | 0             |
| Perineal pain                            |                  |                 |               |
| subjects affected / exposed              | 0 / 17 (0.00%)   | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)                        | 0                | 0               | 0             |
| Testicular oedema                        |                  |                 |               |

|   |                  |                 |               |
|---|------------------|-----------------|---------------|
| subjects affected / exposed                     | 1 / 17 (5.88%)   | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)                               | 1                | 0               | 0             |
| Vaginal haemorrhage                             |                  |                 |               |
| subjects affected / exposed                     | 1 / 17 (5.88%)   | 1 / 22 (4.55%)  | 0 / 1 (0.00%) |
| occurrences (all)                               | 5                | 2               | 0             |
| Vulvovaginal pain                               |                  |                 |               |
| subjects affected / exposed                     | 1 / 17 (5.88%)   | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)                               | 1                | 0               | 0             |
| Respiratory, thoracic and mediastinal disorders |                  |                 |               |
| Bradypnoea                                      |                  |                 |               |
| subjects affected / exposed                     | 0 / 17 (0.00%)   | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)                               | 0                | 0               | 0             |
| Cough   |                  |                 |               |
| subjects affected / exposed                     | 10 / 17 (58.82%) | 3 / 22 (13.64%) | 0 / 1 (0.00%) |
| occurrences (all)                               | 17               | 4               | 0             |
| Dysphonia                                       |                  |                 |               |
| subjects affected / exposed                     | 0 / 17 (0.00%)   | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)                               | 0                | 0               | 0             |
| Epistaxis                                       |                  |                 |               |
| subjects affected / exposed                     | 2 / 17 (11.76%)  | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)                               | 2                | 0               | 0             |
| Hiccups   |                  |                 |               |
| subjects affected / exposed                     | 1 / 17 (5.88%)   | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)                               | 2                | 0               | 0             |
| Laryngeal inflammation                          |                  |                 |               |
| subjects affected / exposed                     | 1 / 17 (5.88%)   | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)                               | 1                | 0               | 0             |
| Nasal congestion                                |                  |                 |               |
| subjects affected / exposed                     | 1 / 17 (5.88%)   | 3 / 22 (13.64%) | 0 / 1 (0.00%) |
| occurrences (all)                               | 6                | 3               | 0             |
| Nasal obstruction                               |                  |                 |               |
| subjects affected / exposed                     | 0 / 17 (0.00%)   | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)                               | 0                | 0               | 0             |
| Oropharyngeal pain                              |                  |                 |               |

|   |                 |                |               |
|---|-----------------|----------------|---------------|
| subjects affected / exposed                     | 3 / 17 (17.65%) | 2 / 22 (9.09%) | 0 / 1 (0.00%) |
| occurrences (all)                               | 5               | 3              | 0             |
| Pharyngeal erythema                             |                 |                |               |
| subjects affected / exposed                     | 1 / 17 (5.88%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                               | 1               | 0              | 0             |
| Rhinitis allergic                               |                 |                |               |
| subjects affected / exposed                     | 1 / 17 (5.88%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                               | 1               | 0              | 0             |
| Tachypnoea                                      |                 |                |               |
| subjects affected / exposed                     | 0 / 17 (0.00%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                               | 0               | 0              | 0             |
| Tonsillolith                                    |                 |                |               |
| subjects affected / exposed                     | 1 / 17 (5.88%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                               | 2               | 0              | 0             |
| Upper respiratory tract inflammation            |                 |                |               |
| subjects affected / exposed                     | 2 / 17 (11.76%) | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                               | 5               | 0              | 0             |
| Psychiatric disorders                           |                 |                |               |
| Anxiety   |                 |                |               |
| subjects affected / exposed                     | 0 / 17 (0.00%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                               | 0               | 0              | 0             |
| Delirium  |                 |                |               |
| subjects affected / exposed                     | 0 / 17 (0.00%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                               | 0               | 0              | 0             |
| Enuresis  |                 |                |               |
| subjects affected / exposed                     | 1 / 17 (5.88%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                               | 1               | 0              | 0             |
| Investigations                                  |                 |                |               |
| Activated partial thromboplastin time prolonged |                 |                |               |
| subjects affected / exposed                     | 0 / 17 (0.00%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                               | 0               | 0              | 0             |
| Alanine aminotransferase increased              |                 |                |               |
| subjects affected / exposed                     | 0 / 17 (0.00%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                               | 0               | 0              | 0             |
| Anion gap                                       |                 |                |               |

|                                       |                 |                |               |
|---------------------------------------|-----------------|----------------|---------------|
| subjects affected / exposed           | 0 / 17 (0.00%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                     | 0               | 0              | 0             |
| Aspartate aminotransferase increased  |                 |                |               |
| subjects affected / exposed           | 2 / 17 (11.76%) | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                     | 3               | 0              | 0             |
| Blood bicarbonate decreased           |                 |                |               |
| subjects affected / exposed           | 0 / 17 (0.00%)  | 1 / 22 (4.55%) | 0 / 1 (0.00%) |
| occurrences (all)                     | 0               | 1              | 0             |
| Blood cholesterol increased           |                 |                |               |
| subjects affected / exposed           | 2 / 17 (11.76%) | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                     | 2               | 0              | 0             |
| Blood fibrinogen increased            |                 |                |               |
| subjects affected / exposed           | 1 / 17 (5.88%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                     | 1               | 0              | 0             |
| Blood insulin increased               |                 |                |               |
| subjects affected / exposed           | 2 / 17 (11.76%) | 2 / 22 (9.09%) | 0 / 1 (0.00%) |
| occurrences (all)                     | 3               | 2              | 0             |
| Blood lactate dehydrogenase increased |                 |                |               |
| subjects affected / exposed           | 0 / 17 (0.00%)  | 2 / 22 (9.09%) | 0 / 1 (0.00%) |
| occurrences (all)                     | 0               | 2              | 0             |
| Bone density decreased                |                 |                |               |
| subjects affected / exposed           | 1 / 17 (5.88%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                     | 1               | 0              | 0             |
| C-reactive protein increased          |                 |                |               |
| subjects affected / exposed           | 0 / 17 (0.00%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                     | 0               | 0              | 0             |
| Electrocardiogram QT prolonged        |                 |                |               |
| subjects affected / exposed           | 0 / 17 (0.00%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                     | 0               | 0              | 0             |
| Fibrin D dimer decreased              |                 |                |               |
| subjects affected / exposed           | 0 / 17 (0.00%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                     | 0               | 0              | 0             |
| Fibrin D dimer increased              |                 |                |               |

|                                   |                 |                |               |
|-----------------------------------|-----------------|----------------|---------------|
| subjects affected / exposed       | 1 / 17 (5.88%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                 | 1               | 0              | 0             |
| Haematocrit increased             |                 |                |               |
| subjects affected / exposed       | 0 / 17 (0.00%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                 | 0               | 0              | 0             |
| Haemoglobin increased             |                 |                |               |
| subjects affected / exposed       | 1 / 17 (5.88%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                 | 1               | 0              | 0             |
| Low density lipoprotein increased |                 |                |               |
| subjects affected / exposed       | 0 / 17 (0.00%)  | 1 / 22 (4.55%) | 0 / 1 (0.00%) |
| occurrences (all)                 | 0               | 1              | 0             |
| Lymphocyte count decreased        |                 |                |               |
| subjects affected / exposed       | 2 / 17 (11.76%) | 1 / 22 (4.55%) | 0 / 1 (0.00%) |
| occurrences (all)                 | 8               | 1              | 0             |
| Lymphocyte count increased        |                 |                |               |
| subjects affected / exposed       | 1 / 17 (5.88%)  | 1 / 22 (4.55%) | 0 / 1 (0.00%) |
| occurrences (all)                 | 3               | 1              | 0             |
| Monocyte count decreased          |                 |                |               |
| subjects affected / exposed       | 1 / 17 (5.88%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                 | 1               | 0              | 0             |
| Neutrophil count decreased        |                 |                |               |
| subjects affected / exposed       | 4 / 17 (23.53%) | 1 / 22 (4.55%) | 0 / 1 (0.00%) |
| occurrences (all)                 | 17              | 2              | 0             |
| Neutrophil count increased        |                 |                |               |
| subjects affected / exposed       | 0 / 17 (0.00%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                 | 0               | 0              | 0             |
| Platelet count decreased          |                 |                |               |
| subjects affected / exposed       | 3 / 17 (17.65%) | 1 / 22 (4.55%) | 0 / 1 (0.00%) |
| occurrences (all)                 | 5               | 1              | 0             |
| Platelet count increased          |                 |                |               |
| subjects affected / exposed       | 0 / 17 (0.00%)  | 1 / 22 (4.55%) | 0 / 1 (0.00%) |
| occurrences (all)                 | 0               | 2              | 0             |
| SARS-CoV-2 test positive          |                 |                |               |
| subjects affected / exposed       | 0 / 17 (0.00%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                 | 0               | 0              | 0             |
| Urine ketone body present         |                 |                |               |

|  |                 |                |               |
|--|-----------------|----------------|---------------|
| subjects affected / exposed                    | 0 / 17 (0.00%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                              | 0               | 0              | 0             |
| Weight decreased                               |                 |                |               |
| subjects affected / exposed                    | 0 / 17 (0.00%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                              | 0               | 0              | 0             |
| White blood cell count decreased               |                 |                |               |
| subjects affected / exposed                    | 2 / 17 (11.76%) | 1 / 22 (4.55%) | 0 / 1 (0.00%) |
| occurrences (all)                              | 3               | 1              | 0             |
| White blood cell count increased               |                 |                |               |
| subjects affected / exposed                    | 0 / 17 (0.00%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                              | 0               | 0              | 0             |
| Injury, poisoning and procedural complications |                 |                |               |
| Contusion                                      |                 |                |               |
| subjects affected / exposed                    | 1 / 17 (5.88%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                              | 4               | 0              | 0             |
| Fall   |                 |                |               |
| subjects affected / exposed                    | 1 / 17 (5.88%)  | 1 / 22 (4.55%) | 0 / 1 (0.00%) |
| occurrences (all)                              | 1               | 1              | 0             |
| Head injury                                    |                 |                |               |
| subjects affected / exposed                    | 1 / 17 (5.88%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                              | 1               | 0              | 0             |
| Injury   |                 |                |               |
| subjects affected / exposed                    | 1 / 17 (5.88%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                              | 1               | 0              | 0             |
| Limb injury                                    |                 |                |               |
| subjects affected / exposed                    | 1 / 17 (5.88%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                              | 1               | 0              | 0             |
| Scratch  |                 |                |               |
| subjects affected / exposed                    | 1 / 17 (5.88%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                              | 1               | 0              | 0             |
| Wound dehiscence                               |                 |                |               |
| subjects affected / exposed                    | 1 / 17 (5.88%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                              | 1               | 0              | 0             |
| Congenital, familial and genetic disorders     |                 |                |               |

|                             |                 |                 |               |
|-----------------------------|-----------------|-----------------|---------------|
| Phimosis                    |                 |                 |               |
| subjects affected / exposed | 1 / 17 (5.88%)  | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 1               | 0               | 0             |
| Vascular malformation       |                 |                 |               |
| subjects affected / exposed | 1 / 17 (5.88%)  | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 1               | 0               | 0             |
| Cardiac disorders           |                 |                 |               |
| Palpitations                |                 |                 |               |
| subjects affected / exposed | 1 / 17 (5.88%)  | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 1               | 0               | 0             |
| Sinus bradycardia           |                 |                 |               |
| subjects affected / exposed | 0 / 17 (0.00%)  | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 0               | 0               | 0             |
| Sinus tachycardia           |                 |                 |               |
| subjects affected / exposed | 0 / 17 (0.00%)  | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 0               | 0               | 0             |
| Tachycardia                 |                 |                 |               |
| subjects affected / exposed | 0 / 17 (0.00%)  | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 0               | 0               | 0             |
| Nervous system disorders    |                 |                 |               |
| Dizziness                   |                 |                 |               |
| subjects affected / exposed | 1 / 17 (5.88%)  | 3 / 22 (13.64%) | 0 / 1 (0.00%) |
| occurrences (all)           | 3               | 5               | 0             |
| Headache                    |                 |                 |               |
| subjects affected / exposed | 3 / 17 (17.65%) | 2 / 22 (9.09%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 9               | 3               | 0             |
| Paraesthesia                |                 |                 |               |
| subjects affected / exposed | 1 / 17 (5.88%)  | 1 / 22 (4.55%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 1               | 1               | 0             |
| Petit mal epilepsy          |                 |                 |               |
| subjects affected / exposed | 1 / 17 (5.88%)  | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 4               | 0               | 0             |
| Presyncope                  |                 |                 |               |
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 3               | 0               | 0             |
| Sciatica                    |                 |                 |               |



|                                      |                 |                |               |
|--------------------------------------|-----------------|----------------|---------------|
| subjects affected / exposed          | 1 / 17 (5.88%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                    | 1               | 0              | 0             |
| Syncope                              |                 |                |               |
| subjects affected / exposed          | 1 / 17 (5.88%)  | 1 / 22 (4.55%) | 0 / 1 (0.00%) |
| occurrences (all)                    | 1               | 1              | 0             |
| Blood and lymphatic system disorders |                 |                |               |
| Anaemia                              |                 |                |               |
| subjects affected / exposed          | 2 / 17 (11.76%) | 1 / 22 (4.55%) | 0 / 1 (0.00%) |
| occurrences (all)                    | 4               | 3              | 0             |
| Eosinophilia                         |                 |                |               |
| subjects affected / exposed          | 1 / 17 (5.88%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                    | 2               | 0              | 0             |
| Immune thrombocytopenia              |                 |                |               |
| subjects affected / exposed          | 1 / 17 (5.88%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                    | 1               | 0              | 0             |
| Iron deficiency anaemia              |                 |                |               |
| subjects affected / exposed          | 0 / 17 (0.00%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                    | 0               | 0              | 0             |
| Neutropenia                          |                 |                |               |
| subjects affected / exposed          | 0 / 17 (0.00%)  | 2 / 22 (9.09%) | 0 / 1 (0.00%) |
| occurrences (all)                    | 0               | 2              | 0             |
| Thrombocytopenia                     |                 |                |               |
| subjects affected / exposed          | 1 / 17 (5.88%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                    | 2               | 0              | 0             |
| Ear and labyrinth disorders          |                 |                |               |
| Excessive cerumen production         |                 |                |               |
| subjects affected / exposed          | 1 / 17 (5.88%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                    | 1               | 0              | 0             |
| Ear pain                             |                 |                |               |
| subjects affected / exposed          | 2 / 17 (11.76%) | 1 / 22 (4.55%) | 0 / 1 (0.00%) |
| occurrences (all)                    | 3               | 1              | 0             |
| Vertigo                              |                 |                |               |
| subjects affected / exposed          | 1 / 17 (5.88%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                    | 1               | 0              | 0             |
| Eye disorders                        |                 |                |               |

|   |                       |                     |                    |
|---|-----------------------|---------------------|--------------------|
| Conjunctival hyperaemia<br>subjects affected / exposed<br>occurrences (all) | 1 / 17 (5.88%)<br>1   | 0 / 22 (0.00%)<br>0 | 0 / 1 (0.00%)<br>0 |
| Erythema of eyelid<br>subjects affected / exposed<br>occurrences (all)      | 1 / 17 (5.88%)<br>1   | 0 / 22 (0.00%)<br>0 | 0 / 1 (0.00%)<br>0 |
| Eye discharge<br>subjects affected / exposed<br>occurrences (all)           | 1 / 17 (5.88%)<br>1   | 0 / 22 (0.00%)<br>0 | 0 / 1 (0.00%)<br>0 |
| Eyelid oedema<br>subjects affected / exposed<br>occurrences (all)           | 1 / 17 (5.88%)<br>1   | 0 / 22 (0.00%)<br>0 | 0 / 1 (0.00%)<br>0 |
| Gastrointestinal disorders  |                       |                     |                    |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)          | 7 / 17 (41.18%)<br>11 | 2 / 22 (9.09%)<br>5 | 0 / 1 (0.00%)<br>0 |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)    | 3 / 17 (17.65%)<br>3  | 0 / 22 (0.00%)<br>0 | 0 / 1 (0.00%)<br>0 |
| Aphthous ulcer<br>subjects affected / exposed<br>occurrences (all)          | 4 / 17 (23.53%)<br>4  | 0 / 22 (0.00%)<br>0 | 0 / 1 (0.00%)<br>0 |
| Constipation<br>subjects affected / exposed<br>occurrences (all)            | 6 / 17 (35.29%)<br>20 | 1 / 22 (4.55%)<br>1 | 0 / 1 (0.00%)<br>0 |
| Cheilitis<br>subjects affected / exposed<br>occurrences (all)               | 0 / 17 (0.00%)<br>0   | 0 / 22 (0.00%)<br>0 | 0 / 1 (0.00%)<br>0 |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)               | 8 / 17 (47.06%)<br>12 | 2 / 22 (9.09%)<br>3 | 0 / 1 (0.00%)<br>0 |
| Dental caries<br>subjects affected / exposed<br>occurrences (all)           | 1 / 17 (5.88%)<br>1   | 1 / 22 (4.55%)<br>1 | 0 / 1 (0.00%)<br>0 |
| Dry mouth   |                       |                     |                    |

|                             |                 |                 |               |
|-----------------------------|-----------------|-----------------|---------------|
| subjects affected / exposed | 0 / 17 (0.00%)  | 2 / 22 (9.09%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 0               | 2               | 0             |
| Food poisoning              |                 |                 |               |
| subjects affected / exposed | 1 / 17 (5.88%)  | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 1               | 0               | 0             |
| Frequent bowel movements    |                 |                 |               |
| subjects affected / exposed | 0 / 17 (0.00%)  | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 0               | 0               | 0             |
| Haematochezia               |                 |                 |               |
| subjects affected / exposed | 0 / 17 (0.00%)  | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 0               | 0               | 0             |
| Mouth haemorrhage           |                 |                 |               |
| subjects affected / exposed | 0 / 17 (0.00%)  | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 0               | 0               | 0             |
| Nausea                      |                 |                 |               |
| subjects affected / exposed | 1 / 17 (5.88%)  | 4 / 22 (18.18%) | 0 / 1 (0.00%) |
| occurrences (all)           | 1               | 6               | 0             |
| Oral pain                   |                 |                 |               |
| subjects affected / exposed | 0 / 17 (0.00%)  | 3 / 22 (13.64%) | 0 / 1 (0.00%) |
| occurrences (all)           | 0               | 3               | 0             |
| Salivary duct obstruction   |                 |                 |               |
| subjects affected / exposed | 0 / 17 (0.00%)  | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 0               | 0               | 0             |
| Rectal haemorrhage          |                 |                 |               |
| subjects affected / exposed | 1 / 17 (5.88%)  | 1 / 22 (4.55%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 5               | 1               | 0             |
| Stomatitis                  |                 |                 |               |
| subjects affected / exposed | 2 / 17 (11.76%) | 4 / 22 (18.18%) | 0 / 1 (0.00%) |
| occurrences (all)           | 2               | 6               | 0             |
| Swollen tongue              |                 |                 |               |
| subjects affected / exposed | 0 / 17 (0.00%)  | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 0               | 0               | 0             |
| Toothache                   |                 |                 |               |
| subjects affected / exposed | 0 / 17 (0.00%)  | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 0               | 0               | 0             |
| Vomiting                    |                 |                 |               |

|  |                        |                       |                    |
|--|------------------------|-----------------------|--------------------|
| subjects affected / exposed<br>occurrences (all) | 11 / 17 (64.71%)<br>24 | 5 / 22 (22.73%)<br>13 | 0 / 1 (0.00%)<br>0 |
| Hepatobiliary disorders                          |                        |                       |                    |
| Hypertransaminasaemia                            |                        |                       |                    |
| subjects affected / exposed                      | 1 / 17 (5.88%)         | 0 / 22 (0.00%)        | 0 / 1 (0.00%)      |
| occurrences (all)                                | 2                      | 0                     | 0                  |
| Skin and subcutaneous tissue disorders           |                        |                       |                    |
| Alopecia   |                        |                       |                    |
| subjects affected / exposed                      | 1 / 17 (5.88%)         | 0 / 22 (0.00%)        | 0 / 1 (0.00%)      |
| occurrences (all)                                | 1                      | 0                     | 0                  |
| Blister  |                        |                       |                    |
| subjects affected / exposed                      | 1 / 17 (5.88%)         | 0 / 22 (0.00%)        | 0 / 1 (0.00%)      |
| occurrences (all)                                | 1                      | 0                     | 0                  |
| Bullous haemorrhagic dermatosis                  |                        |                       |                    |
| subjects affected / exposed                      | 1 / 17 (5.88%)         | 1 / 22 (4.55%)        | 0 / 1 (0.00%)      |
| occurrences (all)                                | 3                      | 1                     | 0                  |
| Dermatitis                                       |                        |                       |                    |
| subjects affected / exposed                      | 1 / 17 (5.88%)         | 0 / 22 (0.00%)        | 0 / 1 (0.00%)      |
| occurrences (all)                                | 1                      | 0                     | 0                  |
| Dry skin   |                        |                       |                    |
| subjects affected / exposed                      | 1 / 17 (5.88%)         | 2 / 22 (9.09%)        | 0 / 1 (0.00%)      |
| occurrences (all)                                | 1                      | 2                     | 0                  |
| Eczema   |                        |                       |                    |
| subjects affected / exposed                      | 2 / 17 (11.76%)        | 1 / 22 (4.55%)        | 0 / 1 (0.00%)      |
| occurrences (all)                                | 4                      | 2                     | 0                  |
| Perioral dermatitis                              |                        |                       |                    |
| subjects affected / exposed                      | 1 / 17 (5.88%)         | 0 / 22 (0.00%)        | 0 / 1 (0.00%)      |
| occurrences (all)                                | 1                      | 0                     | 0                  |
| Petechiae  |                        |                       |                    |
| subjects affected / exposed                      | 1 / 17 (5.88%)         | 0 / 22 (0.00%)        | 0 / 1 (0.00%)      |
| occurrences (all)                                | 1                      | 0                     | 0                  |
| Photosensitivity reaction                        |                        |                       |                    |
| subjects affected / exposed                      | 0 / 17 (0.00%)         | 0 / 22 (0.00%)        | 0 / 1 (0.00%)      |
| occurrences (all)                                | 0                      | 0                     | 0                  |
| Pityriasis rosea                                 |                        |                       |                    |

|                             |                 |                |               |
|-----------------------------|-----------------|----------------|---------------|
| subjects affected / exposed | 1 / 17 (5.88%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)           | 1               | 0              | 0             |
| Rash                        |                 |                |               |
| subjects affected / exposed | 2 / 17 (11.76%) | 2 / 22 (9.09%) | 0 / 1 (0.00%) |
| occurrences (all)           | 2               | 4              | 0             |
| Rash maculo-papular         |                 |                |               |
| subjects affected / exposed | 5 / 17 (29.41%) | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)           | 7               | 0              | 0             |
| Skin disorder               |                 |                |               |
| subjects affected / exposed | 1 / 17 (5.88%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)           | 1               | 0              | 0             |
| Skin hyperpigmentation      |                 |                |               |
| subjects affected / exposed | 0 / 17 (0.00%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)           | 0               | 0              | 0             |
| Skin hypopigmentation       |                 |                |               |
| subjects affected / exposed | 0 / 17 (0.00%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)           | 0               | 0              | 0             |
| Skin irritation             |                 |                |               |
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)           | 2               | 0              | 0             |
| Skin lesion                 |                 |                |               |
| subjects affected / exposed | 3 / 17 (17.65%) | 1 / 22 (4.55%) | 0 / 1 (0.00%) |
| occurrences (all)           | 3               | 1              | 0             |
| Skin mass                   |                 |                |               |
| subjects affected / exposed | 1 / 17 (5.88%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)           | 2               | 0              | 0             |
| Skin ulcer                  |                 |                |               |
| subjects affected / exposed | 1 / 17 (5.88%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)           | 3               | 0              | 0             |
| Renal and urinary disorders |                 |                |               |
| Haematuria                  |                 |                |               |
| subjects affected / exposed | 1 / 17 (5.88%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)           | 1               | 0              | 0             |
| Proteinuria                 |                 |                |               |
| subjects affected / exposed | 1 / 17 (5.88%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)           | 1               | 0              | 0             |

|   |                 |                |               |
|---|-----------------|----------------|---------------|
| Renal disorder                                  |                 |                |               |
| subjects affected / exposed                     | 1 / 17 (5.88%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                               | 1               | 0              | 0             |
| Urinary retention                               |                 |                |               |
| subjects affected / exposed                     | 0 / 17 (0.00%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                               | 0               | 0              | 0             |
| Musculoskeletal and connective tissue disorders |                 |                |               |
| Arthralgia                                      |                 |                |               |
| subjects affected / exposed                     | 4 / 17 (23.53%) | 2 / 22 (9.09%) | 0 / 1 (0.00%) |
| occurrences (all)                               | 14              | 3              | 0             |
| Back pain                                       |                 |                |               |
| subjects affected / exposed                     | 0 / 17 (0.00%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                               | 0               | 0              | 0             |
| Bone pain                                       |                 |                |               |
| subjects affected / exposed                     | 1 / 17 (5.88%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                               | 1               | 0              | 0             |
| Flank pain                                      |                 |                |               |
| subjects affected / exposed                     | 0 / 17 (0.00%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                               | 0               | 0              | 0             |
| Muscle spasms                                   |                 |                |               |
| subjects affected / exposed                     | 1 / 17 (5.88%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                               | 1               | 0              | 0             |
| Musculoskeletal chest pain                      |                 |                |               |
| subjects affected / exposed                     | 1 / 17 (5.88%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                               | 1               | 0              | 0             |
| Musculoskeletal pain                            |                 |                |               |
| subjects affected / exposed                     | 1 / 17 (5.88%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                               | 1               | 0              | 0             |
| Myalgia   |                 |                |               |
| subjects affected / exposed                     | 0 / 17 (0.00%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                               | 0               | 0              | 0             |
| Osteochondrosis                                 |                 |                |               |
| subjects affected / exposed                     | 0 / 17 (0.00%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)                               | 0               | 0              | 0             |
| Pain in extremity                               |                 |                |               |

|                             |                 |                 |               |
|-----------------------------|-----------------|-----------------|---------------|
| subjects affected / exposed | 5 / 17 (29.41%) | 2 / 22 (9.09%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 27              | 4               | 0             |
| Scoliosis                   |                 |                 |               |
| subjects affected / exposed | 1 / 17 (5.88%)  | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 1               | 0               | 0             |
| Spinal pain                 |                 |                 |               |
| subjects affected / exposed | 1 / 17 (5.88%)  | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 1               | 0               | 0             |
| Infections and infestations |                 |                 |               |
| COVID-19                    |                 |                 |               |
| subjects affected / exposed | 0 / 17 (0.00%)  | 2 / 22 (9.09%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 0               | 2               | 0             |
| Cellulitis                  |                 |                 |               |
| subjects affected / exposed | 1 / 17 (5.88%)  | 4 / 22 (18.18%) | 0 / 1 (0.00%) |
| occurrences (all)           | 2               | 10              | 0             |
| Conjunctivitis              |                 |                 |               |
| subjects affected / exposed | 1 / 17 (5.88%)  | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 1               | 0               | 0             |
| Coxsackie viral infection   |                 |                 |               |
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 2               | 0               | 0             |
| Cystitis                    |                 |                 |               |
| subjects affected / exposed | 1 / 17 (5.88%)  | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 2               | 0               | 0             |
| Eye infection               |                 |                 |               |
| subjects affected / exposed | 1 / 17 (5.88%)  | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 1               | 0               | 0             |
| Fungal skin infection       |                 |                 |               |
| subjects affected / exposed | 1 / 17 (5.88%)  | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 1               | 0               | 0             |
| Gastroenteritis             |                 |                 |               |
| subjects affected / exposed | 4 / 17 (23.53%) | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 8               | 0               | 0             |
| Impetigo                    |                 |                 |               |
| subjects affected / exposed | 3 / 17 (17.65%) | 1 / 22 (4.55%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 3               | 1               | 0             |

|                             |                 |                |               |
|-----------------------------|-----------------|----------------|---------------|
| Infection                   |                 |                |               |
| subjects affected / exposed | 1 / 17 (5.88%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)           | 1               | 0              | 0             |
| Influenza                   |                 |                |               |
| subjects affected / exposed | 1 / 17 (5.88%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)           | 1               | 0              | 0             |
| Laryngitis                  |                 |                |               |
| subjects affected / exposed | 1 / 17 (5.88%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)           | 3               | 0              | 0             |
| Nasopharyngitis             |                 |                |               |
| subjects affected / exposed | 3 / 17 (17.65%) | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)           | 4               | 0              | 0             |
| Otitis media                |                 |                |               |
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)           | 3               | 0              | 0             |
| Otitis media acute          |                 |                |               |
| subjects affected / exposed | 1 / 17 (5.88%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)           | 1               | 0              | 0             |
| Paronychia                  |                 |                |               |
| subjects affected / exposed | 1 / 17 (5.88%)  | 1 / 22 (4.55%) | 0 / 1 (0.00%) |
| occurrences (all)           | 1               | 1              | 0             |
| Pharyngitis                 |                 |                |               |
| subjects affected / exposed | 5 / 17 (29.41%) | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)           | 6               | 0              | 0             |
| Pharyngotonsillitis         |                 |                |               |
| subjects affected / exposed | 1 / 17 (5.88%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)           | 1               | 0              | 0             |
| Rhinitis                    |                 |                |               |
| subjects affected / exposed | 5 / 17 (29.41%) | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)           | 6               | 0              | 0             |
| Scarlet fever               |                 |                |               |
| subjects affected / exposed | 1 / 17 (5.88%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)           | 1               | 0              | 0             |
| Sinusitis                   |                 |                |               |
| subjects affected / exposed | 1 / 17 (5.88%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)           | 2               | 0              | 0             |



|                                    |                 |                 |               |
|------------------------------------|-----------------|-----------------|---------------|
| Soft tissue infection              |                 |                 |               |
| subjects affected / exposed        | 0 / 17 (0.00%)  | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)                  | 0               | 0               | 0             |
| Tonsillitis                        |                 |                 |               |
| subjects affected / exposed        | 1 / 17 (5.88%)  | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)                  | 2               | 0               | 0             |
| Tracheitis                         |                 |                 |               |
| subjects affected / exposed        | 1 / 17 (5.88%)  | 1 / 22 (4.55%)  | 0 / 1 (0.00%) |
| occurrences (all)                  | 1               | 1               | 0             |
| Upper respiratory tract infection  |                 |                 |               |
| subjects affected / exposed        | 3 / 17 (17.65%) | 7 / 22 (31.82%) | 0 / 1 (0.00%) |
| occurrences (all)                  | 6               | 13              | 0             |
| Urinary tract infection            |                 |                 |               |
| subjects affected / exposed        | 1 / 17 (5.88%)  | 2 / 22 (9.09%)  | 0 / 1 (0.00%) |
| occurrences (all)                  | 2               | 3               | 0             |
| Viraemia                           |                 |                 |               |
| subjects affected / exposed        | 0 / 17 (0.00%)  | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)                  | 0               | 0               | 0             |
| Viral infection                    |                 |                 |               |
| subjects affected / exposed        | 0 / 17 (0.00%)  | 2 / 22 (9.09%)  | 0 / 1 (0.00%) |
| occurrences (all)                  | 0               | 2               | 0             |
| Metabolism and nutrition disorders |                 |                 |               |
| Alkalosis                          |                 |                 |               |
| subjects affected / exposed        | 0 / 17 (0.00%)  | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)                  | 0               | 0               | 0             |
| Decreased appetite                 |                 |                 |               |
| subjects affected / exposed        | 2 / 17 (11.76%) | 3 / 22 (13.64%) | 0 / 1 (0.00%) |
| occurrences (all)                  | 2               | 3               | 0             |
| Dehydration                        |                 |                 |               |
| subjects affected / exposed        | 1 / 17 (5.88%)  | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)                  | 1               | 0               | 0             |
| Hyperinsulinaemia                  |                 |                 |               |
| subjects affected / exposed        | 1 / 17 (5.88%)  | 0 / 22 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)                  | 1               | 0               | 0             |
| Hyperkalaemia                      |                 |                 |               |

|                             |                 |                |               |
|-----------------------------|-----------------|----------------|---------------|
| subjects affected / exposed | 2 / 17 (11.76%) | 2 / 22 (9.09%) | 0 / 1 (0.00%) |
| occurrences (all)           | 4               | 5              | 0             |
| Hypermagnesaemia            |                 |                |               |
| subjects affected / exposed | 0 / 17 (0.00%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)           | 0               | 0              | 0             |
| Hyperuricaemia              |                 |                |               |
| subjects affected / exposed | 0 / 17 (0.00%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)           | 0               | 0              | 0             |
| Hypocalcaemia               |                 |                |               |
| subjects affected / exposed | 0 / 17 (0.00%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)           | 0               | 0              | 0             |
| Hypoglycaemia               |                 |                |               |
| subjects affected / exposed | 0 / 17 (0.00%)  | 1 / 22 (4.55%) | 0 / 1 (0.00%) |
| occurrences (all)           | 0               | 1              | 0             |
| Hypokalaemia                |                 |                |               |
| subjects affected / exposed | 0 / 17 (0.00%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)           | 0               | 0              | 0             |
| Hyponatraemia               |                 |                |               |
| subjects affected / exposed | 1 / 17 (5.88%)  | 1 / 22 (4.55%) | 0 / 1 (0.00%) |
| occurrences (all)           | 1               | 1              | 0             |
| Hypophosphataemia           |                 |                |               |
| subjects affected / exposed | 0 / 17 (0.00%)  | 0 / 22 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all)           | 0               | 0              | 0             |
| Vitamin D deficiency        |                 |                |               |
| subjects affected / exposed | 1 / 17 (5.88%)  | 1 / 22 (4.55%) | 0 / 1 (0.00%) |
| occurrences (all)           | 1               | 1              | 0             |

| <b>Non-serious adverse events</b>                                      | Part B: Miransertib<br>PROS/PS (Cohort 3) | Part B: Miransertib<br>Compassionate<br>Use/Expanded<br>Access (Cohort 4) |  |
|--|---|---|--|
| Total subjects affected by non-serious<br>adverse events               |   |   |  |
| subjects affected / exposed  | 6 / 8 (75.00%)                            | 1 / 1 (100.00%)   |  |
| Neoplasms benign, malignant and<br>unspecified (incl cysts and polyps) |   |   |  |
| Haemangioma  |   |   |  |
| subjects affected / exposed  | 0 / 8 (0.00%)                             | 0 / 1 (0.00%)   |  |
| occurrences (all)  | 0   | 0   |  |
| Vascular disorders   |   |   |  |

|  |                |                 |  |
|--|----------------|-----------------|--|
| Deep vein thrombosis                                 |                |                 |  |
| subjects affected / exposed                          | 0 / 8 (0.00%)  | 1 / 1 (100.00%) |  |
| occurrences (all)                                    | 0              | 1               |  |
| Hypertension   |                |                 |  |
| subjects affected / exposed                          | 1 / 8 (12.50%) | 0 / 1 (0.00%)   |  |
| occurrences (all)                                    | 4              | 0               |  |
| Hypotension  |                |                 |  |
| subjects affected / exposed                          | 1 / 8 (12.50%) | 0 / 1 (0.00%)   |  |
| occurrences (all)                                    | 1              | 0               |  |
| Venous haemorrhage                                   |                |                 |  |
| subjects affected / exposed                          | 1 / 8 (12.50%) | 0 / 1 (0.00%)   |  |
| occurrences (all)                                    | 1              | 0               |  |
| Lymphorrhoea   |                |                 |  |
| subjects affected / exposed                          | 1 / 8 (12.50%) | 0 / 1 (0.00%)   |  |
| occurrences (all)                                    | 1              | 0               |  |
| General disorders and administration site conditions |                |                 |  |
| Chest pain   |                |                 |  |
| subjects affected / exposed                          | 0 / 8 (0.00%)  | 0 / 1 (0.00%)   |  |
| occurrences (all)                                    | 0              | 0               |  |
| Asthenia   |                |                 |  |
| subjects affected / exposed                          | 0 / 8 (0.00%)  | 0 / 1 (0.00%)   |  |
| occurrences (all)                                    | 0              | 0               |  |
| Chills   |                |                 |  |
| subjects affected / exposed                          | 2 / 8 (25.00%) | 0 / 1 (0.00%)   |  |
| occurrences (all)                                    | 2              | 0               |  |
| Face oedema  |                |                 |  |
| subjects affected / exposed                          | 1 / 8 (12.50%) | 0 / 1 (0.00%)   |  |
| occurrences (all)                                    | 2              | 0               |  |
| Fatigue  |                |                 |  |
| subjects affected / exposed                          | 2 / 8 (25.00%) | 0 / 1 (0.00%)   |  |
| occurrences (all)                                    | 2              | 0               |  |
| Inflammation   |                |                 |  |
| subjects affected / exposed                          | 0 / 8 (0.00%)  | 0 / 1 (0.00%)   |  |
| occurrences (all)                                    | 0              | 0               |  |
| Influenza like illness                               |                |                 |  |

|  |                |               |  |
|--|----------------|---------------|--|
| subjects affected / exposed              | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)                        | 0              | 0             |  |
| Lithiasis                                |                |               |  |
| subjects affected / exposed              | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)                        | 0              | 0             |  |
| Localised oedema                         |                |               |  |
| subjects affected / exposed              | 2 / 8 (25.00%) | 0 / 1 (0.00%) |  |
| occurrences (all)                        | 3              | 0             |  |
| Mucosal inflammation                     |                |               |  |
| subjects affected / exposed              | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)                        | 0              | 0             |  |
| Non-cardiac chest pain                   |                |               |  |
| subjects affected / exposed              | 2 / 8 (25.00%) | 0 / 1 (0.00%) |  |
| occurrences (all)                        | 2              | 0             |  |
| Oedema peripheral                        |                |               |  |
| subjects affected / exposed              | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)                        | 0              | 0             |  |
| Pain                                     |                |               |  |
| subjects affected / exposed              | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)                        | 1              | 0             |  |
| Pyrexia                                  |                |               |  |
| subjects affected / exposed              | 2 / 8 (25.00%) | 0 / 1 (0.00%) |  |
| occurrences (all)                        | 8              | 0             |  |
| Suprapubic pain                          |                |               |  |
| subjects affected / exposed              | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)                        | 0              | 0             |  |
| Swelling                                 |                |               |  |
| subjects affected / exposed              | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)                        | 0              | 0             |  |
| Thirst                                   |                |               |  |
| subjects affected / exposed              | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)                        | 0              | 0             |  |
| Reproductive system and breast disorders |                |               |  |
| Oedema genital                           |                |               |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 8 (12.50%) | 0 / 1 (0.00%)   |  |
| occurrences (all)                               | 1              | 0               |  |
| Perineal erythema                               |                |                 |  |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 1 (0.00%)   |  |
| occurrences (all)                               | 0              | 0               |  |
| Perineal pain                                   |                |                 |  |
| subjects affected / exposed                     | 1 / 8 (12.50%) | 0 / 1 (0.00%)   |  |
| occurrences (all)                               | 1              | 0               |  |
| Testicular oedema                               |                |                 |  |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 1 (0.00%)   |  |
| occurrences (all)                               | 0              | 0               |  |
| Vaginal haemorrhage                             |                |                 |  |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 1 (0.00%)   |  |
| occurrences (all)                               | 0              | 0               |  |
| Vulvovaginal pain                               |                |                 |  |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 1 (0.00%)   |  |
| occurrences (all)                               | 0              | 0               |  |
| Respiratory, thoracic and mediastinal disorders |                |                 |  |
| Bradypnoea                                      |                |                 |  |
| subjects affected / exposed                     | 1 / 8 (12.50%) | 0 / 1 (0.00%)   |  |
| occurrences (all)                               | 1              | 0               |  |
| Cough   |                |                 |  |
| subjects affected / exposed                     | 2 / 8 (25.00%) | 1 / 1 (100.00%) |  |
| occurrences (all)                               | 4              | 1               |  |
| Dysphonia                                       |                |                 |  |
| subjects affected / exposed                     | 1 / 8 (12.50%) | 0 / 1 (0.00%)   |  |
| occurrences (all)                               | 1              | 0               |  |
| Epistaxis                                       |                |                 |  |
| subjects affected / exposed                     | 3 / 8 (37.50%) | 0 / 1 (0.00%)   |  |
| occurrences (all)                               | 7              | 0               |  |
| Hiccups   |                |                 |  |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 1 (0.00%)   |  |
| occurrences (all)                               | 0              | 0               |  |
| Laryngeal inflammation                          |                |                 |  |

|                                      |                |                 |  |
|--------------------------------------|----------------|-----------------|--|
| subjects affected / exposed          | 0 / 8 (0.00%)  | 0 / 1 (0.00%)   |  |
| occurrences (all)                    | 0              | 0               |  |
| Nasal congestion                     |                |                 |  |
| subjects affected / exposed          | 1 / 8 (12.50%) | 0 / 1 (0.00%)   |  |
| occurrences (all)                    | 4              | 0               |  |
| Nasal obstruction                    |                |                 |  |
| subjects affected / exposed          | 0 / 8 (0.00%)  | 1 / 1 (100.00%) |  |
| occurrences (all)                    | 0              | 1               |  |
| Oropharyngeal pain                   |                |                 |  |
| subjects affected / exposed          | 2 / 8 (25.00%) | 1 / 1 (100.00%) |  |
| occurrences (all)                    | 2              | 1               |  |
| Pharyngeal erythema                  |                |                 |  |
| subjects affected / exposed          | 0 / 8 (0.00%)  | 0 / 1 (0.00%)   |  |
| occurrences (all)                    | 0              | 0               |  |
| Rhinitis allergic                    |                |                 |  |
| subjects affected / exposed          | 2 / 8 (25.00%) | 0 / 1 (0.00%)   |  |
| occurrences (all)                    | 2              | 0               |  |
| Tachypnoea                           |                |                 |  |
| subjects affected / exposed          | 1 / 8 (12.50%) | 0 / 1 (0.00%)   |  |
| occurrences (all)                    | 1              | 0               |  |
| Tonsillolith                         |                |                 |  |
| subjects affected / exposed          | 0 / 8 (0.00%)  | 0 / 1 (0.00%)   |  |
| occurrences (all)                    | 0              | 0               |  |
| Upper respiratory tract inflammation |                |                 |  |
| subjects affected / exposed          | 0 / 8 (0.00%)  | 0 / 1 (0.00%)   |  |
| occurrences (all)                    | 0              | 0               |  |
| Psychiatric disorders                |                |                 |  |
| Anxiety                              |                |                 |  |
| subjects affected / exposed          | 2 / 8 (25.00%) | 0 / 1 (0.00%)   |  |
| occurrences (all)                    | 2              | 0               |  |
| Delirium                             |                |                 |  |
| subjects affected / exposed          | 1 / 8 (12.50%) | 0 / 1 (0.00%)   |  |
| occurrences (all)                    | 1              | 0               |  |
| Enuresis                             |                |                 |  |
| subjects affected / exposed          | 0 / 8 (0.00%)  | 0 / 1 (0.00%)   |  |
| occurrences (all)                    | 0              | 0               |  |

|   |                |               |  |
|---|----------------|---------------|--|
| Investigations                                  |                |               |  |
| Activated partial thromboplastin time prolonged |                |               |  |
| subjects affected / exposed                     | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)                               | 1              | 0             |  |
| Alanine aminotransferase increased              |                |               |  |
| subjects affected / exposed                     | 2 / 8 (25.00%) | 0 / 1 (0.00%) |  |
| occurrences (all)                               | 5              | 0             |  |
| Anion gap                                       |                |               |  |
| subjects affected / exposed                     | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)                               | 1              | 0             |  |
| Aspartate aminotransferase increased            |                |               |  |
| subjects affected / exposed                     | 2 / 8 (25.00%) | 0 / 1 (0.00%) |  |
| occurrences (all)                               | 2              | 0             |  |
| Blood bicarbonate decreased                     |                |               |  |
| subjects affected / exposed                     | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)                               | 1              | 0             |  |
| Blood cholesterol increased                     |                |               |  |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)                               | 0              | 0             |  |
| Blood fibrinogen increased                      |                |               |  |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)                               | 0              | 0             |  |
| Blood insulin increased                         |                |               |  |
| subjects affected / exposed                     | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)                               | 1              | 0             |  |
| Blood lactate dehydrogenase increased           |                |               |  |
| subjects affected / exposed                     | 4 / 8 (50.00%) | 0 / 1 (0.00%) |  |
| occurrences (all)                               | 6              | 0             |  |
| Bone density decreased                          |                |               |  |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)                               | 0              | 0             |  |
| C-reactive protein increased                    |                |               |  |
| subjects affected / exposed                     | 2 / 8 (25.00%) | 0 / 1 (0.00%) |  |
| occurrences (all)                               | 2              | 0             |  |
| Electrocardiogram QT prolonged                  |                |               |  |

|                                   |                |               |  |
|-----------------------------------|----------------|---------------|--|
| subjects affected / exposed       | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)                 | 1              | 0             |  |
| Fibrin D dimer decreased          |                |               |  |
| subjects affected / exposed       | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)                 | 1              | 0             |  |
| Fibrin D dimer increased          |                |               |  |
| subjects affected / exposed       | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)                 | 0              | 0             |  |
| Haematocrit increased             |                |               |  |
| subjects affected / exposed       | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)                 | 1              | 0             |  |
| Haemoglobin increased             |                |               |  |
| subjects affected / exposed       | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)                 | 0              | 0             |  |
| Low density lipoprotein increased |                |               |  |
| subjects affected / exposed       | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)                 | 1              | 0             |  |
| Lymphocyte count decreased        |                |               |  |
| subjects affected / exposed       | 4 / 8 (50.00%) | 0 / 1 (0.00%) |  |
| occurrences (all)                 | 10             | 0             |  |
| Lymphocyte count increased        |                |               |  |
| subjects affected / exposed       | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)                 | 0              | 0             |  |
| Monocyte count decreased          |                |               |  |
| subjects affected / exposed       | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)                 | 0              | 0             |  |
| Neutrophil count decreased        |                |               |  |
| subjects affected / exposed       | 3 / 8 (37.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)                 | 5              | 0             |  |
| Neutrophil count increased        |                |               |  |
| subjects affected / exposed       | 2 / 8 (25.00%) | 0 / 1 (0.00%) |  |
| occurrences (all)                 | 3              | 0             |  |
| Platelet count decreased          |                |               |  |
| subjects affected / exposed       | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)                 | 1              | 0             |  |
| Platelet count increased          |                |               |  |



|  |                |               |  |
|--|----------------|---------------|--|
| subjects affected / exposed                    | 2 / 8 (25.00%) | 0 / 1 (0.00%) |  |
| occurrences (all)                              | 4              | 0             |  |
| SARS-CoV-2 test positive                       |                |               |  |
| subjects affected / exposed                    | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)                              | 2              | 0             |  |
| Urine ketone body present                      |                |               |  |
| subjects affected / exposed                    | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)                              | 1              | 0             |  |
| Weight decreased                               |                |               |  |
| subjects affected / exposed                    | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)                              | 3              | 0             |  |
| White blood cell count decreased               |                |               |  |
| subjects affected / exposed                    | 2 / 8 (25.00%) | 0 / 1 (0.00%) |  |
| occurrences (all)                              | 5              | 0             |  |
| White blood cell count increased               |                |               |  |
| subjects affected / exposed                    | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)                              | 1              | 0             |  |
| Injury, poisoning and procedural complications |                |               |  |
| Contusion                                      |                |               |  |
| subjects affected / exposed                    | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)                              | 0              | 0             |  |
| Fall   |                |               |  |
| subjects affected / exposed                    | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)                              | 0              | 0             |  |
| Head injury                                    |                |               |  |
| subjects affected / exposed                    | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)                              | 0              | 0             |  |
| Injury   |                |               |  |
| subjects affected / exposed                    | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)                              | 0              | 0             |  |
| Limb injury                                    |                |               |  |
| subjects affected / exposed                    | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)                              | 0              | 0             |  |
| Scratch  |                |               |  |

|  |                     |                    |  |
|--|---------------------|--------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 0 / 8 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 |  |
| Wound dehiscence<br>subjects affected / exposed<br>occurrences (all)                                       | 0 / 8 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 |  |
| Congenital, familial and genetic disorders<br>Phimosis<br>subjects affected / exposed<br>occurrences (all) | 0 / 8 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 |  |
| Vascular malformation<br>subjects affected / exposed<br>occurrences (all)                                  | 0 / 8 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 |  |
| Cardiac disorders<br>Palpitations<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 8 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 |  |
| Sinus bradycardia<br>subjects affected / exposed<br>occurrences (all)                                      | 2 / 8 (25.00%)<br>2 | 0 / 1 (0.00%)<br>0 |  |
| Sinus tachycardia<br>subjects affected / exposed<br>occurrences (all)                                      | 2 / 8 (25.00%)<br>2 | 0 / 1 (0.00%)<br>0 |  |
| Tachycardia<br>subjects affected / exposed<br>occurrences (all)  | 1 / 8 (12.50%)<br>2 | 0 / 1 (0.00%)<br>0 |  |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)                  | 3 / 8 (37.50%)<br>3 | 0 / 1 (0.00%)<br>0 |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)   | 2 / 8 (25.00%)<br>3 | 0 / 1 (0.00%)<br>0 |  |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 8 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 |  |
| Petit mal epilepsy   |                     |                    |  |

|                                      |                |                 |  |
|--------------------------------------|----------------|-----------------|--|
| subjects affected / exposed          | 0 / 8 (0.00%)  | 0 / 1 (0.00%)   |  |
| occurrences (all)                    | 0              | 0               |  |
| Presyncope                           |                |                 |  |
| subjects affected / exposed          | 0 / 8 (0.00%)  | 0 / 1 (0.00%)   |  |
| occurrences (all)                    | 0              | 0               |  |
| Sciatica                             |                |                 |  |
| subjects affected / exposed          | 0 / 8 (0.00%)  | 0 / 1 (0.00%)   |  |
| occurrences (all)                    | 0              | 0               |  |
| Syncope                              |                |                 |  |
| subjects affected / exposed          | 0 / 8 (0.00%)  | 1 / 1 (100.00%) |  |
| occurrences (all)                    | 0              | 1               |  |
| Blood and lymphatic system disorders |                |                 |  |
| Anaemia                              |                |                 |  |
| subjects affected / exposed          | 2 / 8 (25.00%) | 0 / 1 (0.00%)   |  |
| occurrences (all)                    | 6              | 0               |  |
| Eosinophilia                         |                |                 |  |
| subjects affected / exposed          | 2 / 8 (25.00%) | 0 / 1 (0.00%)   |  |
| occurrences (all)                    | 3              | 0               |  |
| Immune thrombocytopenia              |                |                 |  |
| subjects affected / exposed          | 0 / 8 (0.00%)  | 0 / 1 (0.00%)   |  |
| occurrences (all)                    | 0              | 0               |  |
| Iron deficiency anaemia              |                |                 |  |
| subjects affected / exposed          | 1 / 8 (12.50%) | 0 / 1 (0.00%)   |  |
| occurrences (all)                    | 1              | 0               |  |
| Neutropenia                          |                |                 |  |
| subjects affected / exposed          | 0 / 8 (0.00%)  | 0 / 1 (0.00%)   |  |
| occurrences (all)                    | 0              | 0               |  |
| Thrombocytopenia                     |                |                 |  |
| subjects affected / exposed          | 0 / 8 (0.00%)  | 0 / 1 (0.00%)   |  |
| occurrences (all)                    | 0              | 0               |  |
| Ear and labyrinth disorders          |                |                 |  |
| Excessive cerumen production         |                |                 |  |
| subjects affected / exposed          | 0 / 8 (0.00%)  | 0 / 1 (0.00%)   |  |
| occurrences (all)                    | 0              | 0               |  |
| Ear pain                             |                |                 |  |

|                             |                |               |  |
|-----------------------------|----------------|---------------|--|
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)           | 0              | 0             |  |
| Vertigo                     |                |               |  |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)           | 0              | 0             |  |
| Eye disorders               |                |               |  |
| Conjunctival hyperaemia     |                |               |  |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)           | 0              | 0             |  |
| Erythema of eyelid          |                |               |  |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)           | 0              | 0             |  |
| Eye discharge               |                |               |  |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)           | 0              | 0             |  |
| Eyelid oedema               |                |               |  |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)           | 0              | 0             |  |
| Gastrointestinal disorders  |                |               |  |
| Abdominal pain              |                |               |  |
| subjects affected / exposed | 4 / 8 (50.00%) | 0 / 1 (0.00%) |  |
| occurrences (all)           | 7              | 0             |  |
| Abdominal pain upper        |                |               |  |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)           | 0              | 0             |  |
| Aphthous ulcer              |                |               |  |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)           | 0              | 0             |  |
| Constipation                |                |               |  |
| subjects affected / exposed | 3 / 8 (37.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)           | 4              | 0             |  |
| Cheilitis                   |                |               |  |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)           | 1              | 0             |  |
| Diarrhoea                   |                |               |  |

|                             |                |               |
|-----------------------------|----------------|---------------|
| subjects affected / exposed | 4 / 8 (50.00%) | 0 / 1 (0.00%) |
| occurrences (all)           | 10             | 0             |
| Dental caries               |                |               |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 0              | 0             |
| Dry mouth                   |                |               |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 0              | 0             |
| Food poisoning              |                |               |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 1 (0.00%) |
| occurrences (all)           | 1              | 0             |
| Frequent bowel movements    |                |               |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 1 (0.00%) |
| occurrences (all)           | 1              | 0             |
| Haematochezia               |                |               |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 1 (0.00%) |
| occurrences (all)           | 1              | 0             |
| Mouth haemorrhage           |                |               |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 1 (0.00%) |
| occurrences (all)           | 5              | 0             |
| Nausea                      |                |               |
| subjects affected / exposed | 3 / 8 (37.50%) | 0 / 1 (0.00%) |
| occurrences (all)           | 7              | 0             |
| Oral pain                   |                |               |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 1 (0.00%) |
| occurrences (all)           | 4              | 0             |
| Salivary duct obstruction   |                |               |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 1 (0.00%) |
| occurrences (all)           | 1              | 0             |
| Rectal haemorrhage          |                |               |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 0              | 0             |
| Stomatitis                  |                |               |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 1 (0.00%) |
| occurrences (all)           | 3              | 0             |
| Swollen tongue              |                |               |

|  |                |                 |  |
|--|----------------|-----------------|--|
| subjects affected / exposed            | 1 / 8 (12.50%) | 0 / 1 (0.00%)   |  |
| occurrences (all)                      | 1              | 0               |  |
| Toothache                              |                |                 |  |
| subjects affected / exposed            | 1 / 8 (12.50%) | 0 / 1 (0.00%)   |  |
| occurrences (all)                      | 1              | 0               |  |
| Vomiting                               |                |                 |  |
| subjects affected / exposed            | 2 / 8 (25.00%) | 1 / 1 (100.00%) |  |
| occurrences (all)                      | 6              | 1               |  |
| Hepatobiliary disorders                |                |                 |  |
| Hypertransaminasaemia                  |                |                 |  |
| subjects affected / exposed            | 0 / 8 (0.00%)  | 0 / 1 (0.00%)   |  |
| occurrences (all)                      | 0              | 0               |  |
| Skin and subcutaneous tissue disorders |                |                 |  |
| Alopecia                               |                |                 |  |
| subjects affected / exposed            | 0 / 8 (0.00%)  | 0 / 1 (0.00%)   |  |
| occurrences (all)                      | 0              | 0               |  |
| Blister                                |                |                 |  |
| subjects affected / exposed            | 0 / 8 (0.00%)  | 0 / 1 (0.00%)   |  |
| occurrences (all)                      | 0              | 0               |  |
| Bullous haemorrhagic dermatosis        |                |                 |  |
| subjects affected / exposed            | 0 / 8 (0.00%)  | 0 / 1 (0.00%)   |  |
| occurrences (all)                      | 0              | 0               |  |
| Dermatitis                             |                |                 |  |
| subjects affected / exposed            | 0 / 8 (0.00%)  | 0 / 1 (0.00%)   |  |
| occurrences (all)                      | 0              | 0               |  |
| Dry skin                               |                |                 |  |
| subjects affected / exposed            | 2 / 8 (25.00%) | 0 / 1 (0.00%)   |  |
| occurrences (all)                      | 3              | 0               |  |
| Eczema                                 |                |                 |  |
| subjects affected / exposed            | 0 / 8 (0.00%)  | 0 / 1 (0.00%)   |  |
| occurrences (all)                      | 0              | 0               |  |
| Perioral dermatitis                    |                |                 |  |
| subjects affected / exposed            | 0 / 8 (0.00%)  | 0 / 1 (0.00%)   |  |
| occurrences (all)                      | 0              | 0               |  |
| Petechiae                              |                |                 |  |

|                             |                |               |  |
|-----------------------------|----------------|---------------|--|
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)           | 0              | 0             |  |
| Photosensitivity reaction   |                |               |  |
| subjects affected / exposed | 2 / 8 (25.00%) | 0 / 1 (0.00%) |  |
| occurrences (all)           | 2              | 0             |  |
| Pityriasis rosea            |                |               |  |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)           | 0              | 0             |  |
| Rash                        |                |               |  |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)           | 0              | 0             |  |
| Rash maculo-papular         |                |               |  |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)           | 1              | 0             |  |
| Skin disorder               |                |               |  |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)           | 0              | 0             |  |
| Skin hyperpigmentation      |                |               |  |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)           | 1              | 0             |  |
| Skin hypopigmentation       |                |               |  |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)           | 1              | 0             |  |
| Skin irritation             |                |               |  |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)           | 0              | 0             |  |
| Skin lesion                 |                |               |  |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)           | 0              | 0             |  |
| Skin mass                   |                |               |  |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)           | 0              | 0             |  |
| Skin ulcer                  |                |               |  |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)           | 0              | 0             |  |
| Renal and urinary disorders |                |               |  |

|   |                |               |  |
|---|----------------|---------------|--|
| Haematuria                                      |                |               |  |
| subjects affected / exposed                     | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)                               | 1              | 0             |  |
| Proteinuria                                     |                |               |  |
| subjects affected / exposed                     | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)                               | 1              | 0             |  |
| Renal disorder                                  |                |               |  |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)                               | 0              | 0             |  |
| Urinary retention                               |                |               |  |
| subjects affected / exposed                     | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)                               | 1              | 0             |  |
| Musculoskeletal and connective tissue disorders |                |               |  |
| Arthralgia                                      |                |               |  |
| subjects affected / exposed                     | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)                               | 1              | 0             |  |
| Back pain                                       |                |               |  |
| subjects affected / exposed                     | 3 / 8 (37.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)                               | 5              | 0             |  |
| Bone pain                                       |                |               |  |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)                               | 0              | 0             |  |
| Flank pain                                      |                |               |  |
| subjects affected / exposed                     | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)                               | 1              | 0             |  |
| Muscle spasms                                   |                |               |  |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)                               | 0              | 0             |  |
| Musculoskeletal chest pain                      |                |               |  |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)                               | 0              | 0             |  |
| Musculoskeletal pain                            |                |               |  |
| subjects affected / exposed                     | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)                               | 2              | 0             |  |
| Myalgia   |                |               |  |



|                             |                |               |  |
|-----------------------------|----------------|---------------|--|
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)           | 1              | 0             |  |
| Osteochondrosis             |                |               |  |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)           | 1              | 0             |  |
| Pain in extremity           |                |               |  |
| subjects affected / exposed | 3 / 8 (37.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)           | 3              | 0             |  |
| Scoliosis                   |                |               |  |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)           | 0              | 0             |  |
| Spinal pain                 |                |               |  |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)           | 0              | 0             |  |
| Infections and infestations |                |               |  |
| COVID-19                    |                |               |  |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)           | 0              | 0             |  |
| Cellulitis                  |                |               |  |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)           | 0              | 0             |  |
| Conjunctivitis              |                |               |  |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)           | 0              | 0             |  |
| Coxsackie viral infection   |                |               |  |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)           | 0              | 0             |  |
| Cystitis                    |                |               |  |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)           | 0              | 0             |  |
| Eye infection               |                |               |  |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)           | 0              | 0             |  |
| Fungal skin infection       |                |               |  |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)           | 1              | 0             |  |

|                             |                |               |
|-----------------------------|----------------|---------------|
| Gastroenteritis             |                |               |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 0              | 0             |
| Impetigo                    |                |               |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 0              | 0             |
| Infection                   |                |               |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 0              | 0             |
| Influenza                   |                |               |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 0              | 0             |
| Laryngitis                  |                |               |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 0              | 0             |
| Nasopharyngitis             |                |               |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 1 (0.00%) |
| occurrences (all)           | 1              | 0             |
| Otitis media                |                |               |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 0              | 0             |
| Otitis media acute          |                |               |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 0              | 0             |
| Paronychia                  |                |               |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 0              | 0             |
| Pharyngitis                 |                |               |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 0              | 0             |
| Pharyngotonsillitis         |                |               |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 0              | 0             |
| Rhinitis                    |                |               |
| subjects affected / exposed | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |
| occurrences (all)           | 0              | 0             |

|                                    |                |               |  |
|------------------------------------|----------------|---------------|--|
| Scarlet fever                      |                |               |  |
| subjects affected / exposed        | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)                  | 0              | 0             |  |
| Sinusitis                          |                |               |  |
| subjects affected / exposed        | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)                  | 0              | 0             |  |
| Soft tissue infection              |                |               |  |
| subjects affected / exposed        | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)                  | 1              | 0             |  |
| Tonsillitis                        |                |               |  |
| subjects affected / exposed        | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)                  | 0              | 0             |  |
| Tracheitis                         |                |               |  |
| subjects affected / exposed        | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)                  | 0              | 0             |  |
| Upper respiratory tract infection  |                |               |  |
| subjects affected / exposed        | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)                  | 2              | 0             |  |
| Urinary tract infection            |                |               |  |
| subjects affected / exposed        | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)                  | 1              | 0             |  |
| Viraemia                           |                |               |  |
| subjects affected / exposed        | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)                  | 1              | 0             |  |
| Viral infection                    |                |               |  |
| subjects affected / exposed        | 0 / 8 (0.00%)  | 0 / 1 (0.00%) |  |
| occurrences (all)                  | 0              | 0             |  |
| Metabolism and nutrition disorders |                |               |  |
| Alkalosis                          |                |               |  |
| subjects affected / exposed        | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)                  | 1              | 0             |  |
| Decreased appetite                 |                |               |  |
| subjects affected / exposed        | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)                  | 5              | 0             |  |
| Dehydration                        |                |               |  |

|                             |                |               |  |
|-----------------------------|----------------|---------------|--|
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)           | 1              | 0             |  |
| Hyperinsulinaemia           |                |               |  |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)           | 1              | 0             |  |
| Hyperkalaemia               |                |               |  |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)           | 2              | 0             |  |
| Hypermagnesaemia            |                |               |  |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)           | 1              | 0             |  |
| Hyperuricaemia              |                |               |  |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)           | 2              | 0             |  |
| Hypocalcaemia               |                |               |  |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)           | 1              | 0             |  |
| Hypoglycaemia               |                |               |  |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)           | 1              | 0             |  |
| Hypokalaemia                |                |               |  |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)           | 1              | 0             |  |
| Hyponatraemia               |                |               |  |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)           | 2              | 0             |  |
| Hypophosphataemia           |                |               |  |
| subjects affected / exposed | 2 / 8 (25.00%) | 0 / 1 (0.00%) |  |
| occurrences (all)           | 3              | 0             |  |
| Vitamin D deficiency        |                |               |  |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 1 (0.00%) |  |
| occurrences (all)           | 1              | 0             |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment   |
|-------------------|---|
| 22 February 2017  | Major changes of Amendment (AM) 1 include modification to the definition of drug related toxicity to include any toxicities considered related, probably related, or possibly related to miransertib, updates to toxicities that prevent dose titrations, updates to dose limiting toxicity criteria for discontinuation of study treatment and modifications to the blood sample collection schedule for pharmacokinetic (PK) evaluation.  |
| 27 July 2017      | Major changes of AM 2 include the possibility to open the miransertib capsule and administering it with a sweetened semiliquid, expanding window to collect overgrowth tissue, include blood sample collection for potential biomarkers during Cycle 1 Day 1 and removing fasting glucose requirements and electrocardiogram (ECG) for Cycle 1 Day 1 and expansion in contraception methods in accordance with clinical trials facilitation and coordination Group (CTFG) guidelines. |
| 13 December 2017  | Major changes of AM 3 include changing the eligibility criteria from 6 years to 2 years of age and removing phosphatase and tensin on chromosome 10 (PTEN) as an eligible mutation, adding of pain scale and to remove PK collection on Day 8, making biopsies optional, adding clarification that maximum dose titrations were not required if efficacy was seen at the lower dose levels and permitting intermittent use of high dose steroids as required.                         |
| 20 September 2018 | Major changes of AM 4 include updating inclusion criteria for participant population extending duration of treatment to 48 cycles and evaluating accumulated outcomes data, allowing surgical procedures as long as the procedures did not meet the discontinuation criteria, and increasing the enrollment number for participants in the study.   |
| 16 September 2019 | Major changes of AM 6 include closing participant enrollment to Part A of the study, including Part B Cohort 4, updating study efficacy and exploratory endpoints, and increasing number of global sites.   |
| 08 October 2021   | Major changes of AM 7 include removing all primary efficacy endpoints and all secondary endpoints, changing sponsor to ArQule, Inc (A Wholly owned subsidiary to Merck Sharp & Dohme, a subsidiary of Merck & Co., Inc), and updating primary objective to reflect safety and tolerability of miransertib.  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date          | Interruption     | Restart date |
|---------------|------------------|--------------|
| 07 March 2022 | Business reasons | -            |

Notes:

### Limitations and caveats

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

Early termination due to business reasons

Notes: