



## Clinical trial results:

**A phase I/randomised phase II trial of abiraterone acetate or enzalutamide with or without idasanutlin (RO5503781) in patients with metastatic castration resistant prostate cancer who have not previously received docetaxel.**

### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2013-002014-13   |
| Trial protocol           | GB               |
| Global end of trial date | 09 December 2019 |

### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 25 December 2020 |
| First version publication date | 25 December 2020 |

### Trial information

#### Trial identification

|                       |            |
|-----------------------|------------|
| Sponsor protocol code | MAdCaP2013 |
|-----------------------|------------|

#### Additional study identifiers

|                                    |                |
|------------------------------------|----------------|
| ISRCTN number                      | ISRCTN38949950 |
| ClinicalTrials.gov id (NCT number) | -              |
| WHO universal trial number (UTN)   | -              |

Notes:

### Sponsors

|                              |                                                                                                                                                     |
|------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | NHS Greater Glasgow & Clyde                                                                                                                         |
| Sponsor organisation address | Ward 11, Dykebar Hospital, Paisley, United Kingdom, PA2 7DE                                                                                         |
| Public contact               | Lorna Sweeting, CRUK Clinical Trials Unit, Beatson West of Scotland Cancer Centre, Glasgow, G12 0YN, 44 0141 301 7194, lorna.sweeting@glasgow.ac.uk |
| Scientific contact           | Lorna Sweeting, CRUK Clinical Trials Unit, Beatson West of Scotland Cancer Centre, Glasgow, G12 0YN, 44 0141 301 7194, lorna.sweeting@glasgow.ac.uk |
| Sponsor organisation name    | University of Glasgow                                                                                                                               |
| Sponsor organisation address | Room 327, Wolfson Medical School Building, Glasgow, United Kingdom, G12 8QQ                                                                         |
| Public contact               | Lorna Sweeting, CRUK Clinical Trials Unit, Beatson West of Scotland Cancer Centre, Glasgow, G12 0YN, 44 0141 301 7194, lorna.sweeting@glasgow.ac.uk |
| Scientific contact           | Lorna Sweeting, CRUK Clinical Trials Unit, Beatson West of Scotland Cancer Centre, Glasgow, G12 0YN, 44 0141 301 7194, lorna.sweeting@glasgow.ac.uk |

Notes:

### Paediatric regulatory details

|                                                                |    |
|----------------------------------------------------------------|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
|----------------------------------------------------------------|----|

|                                                                      |    |
|----------------------------------------------------------------------|----|
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|                                                      |                  |
|------------------------------------------------------|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 09 December 2019 |
| Is this the analysis of the primary completion data? | No               |

|                                  |                  |
|----------------------------------|------------------|
| Global end of trial reached?     | Yes              |
| Global end of trial date         | 09 December 2019 |
| Was the trial ended prematurely? | No               |

Notes:

## General information about the trial

Main objective of the trial:

Primary objective (phase I):

To establish a safe and tolerable dose for RO5503781 given in combination with abiraterone or enzalutamide.

Primary objective (phase II):

To establish whether the efficacy of the combination of RO5503781 with abiraterone and prednisolone or enzalutamide merits further study in patients with mCRPC. The primary endpoint will be radiological progression free survival (please note, our commercial partner Roche decided not to provide support for the planned Phase II component of the study and therefore this did not proceed).

Protection of trial subjects:

Patients were required to attend for visits and investigations that were considered to be additional to standard of care. The number and types of visits and assessments were fully explained verbally and in a Patient Information Sheet which patients were given time to read and discuss with family, and the research team, prior to consent. All staff involved in delivering the study were fully GCP trained. In the dose escalation phase (phase I), patients were reviewed weekly for Dose Limiting Toxicities and a Safety Review Committee met at the completion of each dose cohort to review the patient details and confirm the escalation to the next dose level where appropriate.

Background therapy: -

Evidence for comparator: -

|                                                           |               |
|-----------------------------------------------------------|---------------|
| Actual start date of recruitment                          | 31 March 2014 |
| 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 | United Kingdom: 22 |
| Worldwide total number of subjects   | 22                 |
| EEA total number of subjects         | 22                 |

Notes:

| <b>Subjects enrolled per age group</b>    |    |
|-------------------------------------------|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 16 |
| From 65 to 84 years                       | 6  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Phase I: Open to recruitment between 31st March 2014 and 3rd July 2017 with 22 patients recruited over 6 cohorts.

Phase II: Roche, our commercial partner, decided not to provide support for the Phase II component of the study, therefore this did not proceed and no patients were recruited.

### Pre-assignment

Screening details:

Following consent, all patients underwent screening to determine eligibility, including confirmation of disease progressions, physical exam, blood tests (including testosterone), review of prior treatment (prior cytotoxic chemotherapy excluded, no other anticancer therapy (apart from LHRH agonist/antagonist) within 4 weeks.

### Period 1

|                              |                             |
|------------------------------|-----------------------------|
| Period 1 title               | Phase I (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>             | Cohort -1 |

Arm description:

RO5503781 (Idasanutlin) MBP (microprecipitated bulk powder) tablet formulation, a single dose given orally on day -7, then 200mg orally once daily on days 1-3 of a 28 day cycle with abiraterone orally 1000mg once daily and prednisolone orally 5mg twice a day.

This was repeated every 28 days until progression.

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Idasanutlin  |
| Investigational medicinal product code | RO5503781    |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

RO5503781 (Idasanutlin) MBP (microprecipitated bulk powder) tablet formulation, a single dose given orally on day -7, then 200mg orally once daily on days 1-3 of a 28 day cycle

|                                        |             |
|----------------------------------------|-------------|
| Investigational medicinal product name | Abiraterone |
| Investigational medicinal product code |             |
| Other name                             |             |
| Pharmaceutical forms                   | Tablet      |
| Routes of administration               | Oral use    |

Dosage and administration details:

1000mg orally once a day continuously

|                  |          |
|------------------|----------|
| <b>Arm title</b> | Cohort 1 |
|------------------|----------|

Arm description:

RO5503781 (Idasanutlin) MBP (microprecipitated bulk powder) tablet formulation, a single dose given orally on day -7, then 200mg orally once daily on days 1-5 of a 28 day cycle with abiraterone orally 1000mg once daily and prednisolone orally 5mg twice a day.

This was repeated every 28 days until progression.

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|                                        |             |
|----------------------------------------|-------------|
| Investigational medicinal product name | Idasanutlin |
| Investigational medicinal product code | RO5503781   |
| Other name                             |             |
| Pharmaceutical forms                   | Tablet      |
| Routes of administration               | Oral use    |

Dosage and administration details:

RO5503781 (Idasanutlin) MBP (microprecipitated bulk powder) tablet formulation, a single dose given orally on day -7, then 200mg orally once daily on days 1-5 of a 28 day cycle

|                                        |             |
|----------------------------------------|-------------|
| Investigational medicinal product name | Abiraterone |
| Investigational medicinal product code |             |
| Other name                             |             |
| Pharmaceutical forms                   | Tablet      |
| Routes of administration               | Oral use    |

Dosage and administration details:

1000mg orally once a day continuously

|                  |           |
|------------------|-----------|
| <b>Arm title</b> | Cohort 1* |
|------------------|-----------|

Arm description:

RO5503781 (Idasanutlin) MBP (microprecipitated bulk powder) tablet formulation 200mg orally once daily on days 1-5 of a 28 day cycle with abiraterone orally 1000mg once daily and prednisolone orally 5mg twice a day.

This was repeated every 28 days until progression.

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Idasanutlin  |
| Investigational medicinal product code | RO5503781    |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

RO5503781 (Idasanutlin) MBP (microprecipitated bulk powder) tablet formulation, 200mg orally once daily on days 1-5 of a 28 day cycle

|                                        |             |
|----------------------------------------|-------------|
| Investigational medicinal product name | Abiraterone |
| Investigational medicinal product code |             |
| Other name                             |             |
| Pharmaceutical forms                   | Tablet      |
| Routes of administration               | Oral use    |

Dosage and administration details:

1000mg orally once a day continuously

|                  |          |
|------------------|----------|
| <b>Arm title</b> | Cohort 2 |
|------------------|----------|

Arm description:

RO5503781 (Idasanutlin) MBP (microprecipitated bulk powder) tablet formulation, 400mg orally once daily on days 1-5 of a 28 day cycle with abiraterone orally 1000mg once daily and prednisolone orally 5mg twice a day.

This was repeated every 28 days until progression.

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Idasanutlin  |
| Investigational medicinal product code | RO5503781    |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

RO5503781 (Idasanutlin) MBP (microprecipitated bulk powder) tablet formulation, 400mg orally once daily on days 1-5 of a 28 day cycle

|                                                                             |             |
|-----------------------------------------------------------------------------|-------------|
| Investigational medicinal product name                                      | Abiraterone |
| Investigational medicinal product code                                      |             |
| Other name                                                                  |             |
| Pharmaceutical forms                                                        | Tablet      |
| Routes of administration                                                    | Oral use    |
| Dosage and administration details:<br>1000mg orally once a day continuously |             |
| <b>Arm title</b>                                                            | Cohort 3B   |

Arm description:

RO5503781 (Idasanutlin) SDP (spray-dried powder) tablet formulation, 250mg orally once daily on days 1-5 of a 28 day cycle with abiraterone orally 1000mg once daily and prednisolone orally 5mg twice a day.

This was repeated every 28 days until progression.

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Idasanutlin  |
| Investigational medicinal product code | RO5503781    |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

RO5503781 (Idasanutlin) SDP (spray-dried powder) tablet formulation, 250mg orally once daily on days 1-5 of a 28 day cycle

|                                        |             |
|----------------------------------------|-------------|
| Investigational medicinal product name | Abiraterone |
| Investigational medicinal product code |             |
| Other name                             |             |
| Pharmaceutical forms                   | Tablet      |
| Routes of administration               | Oral use    |

Dosage and administration details:

1000mg orally once a day continuously

|                  |           |
|------------------|-----------|
| <b>Arm title</b> | Cohort 1E |
|------------------|-----------|

Arm description:

RO5503781 (Idasanutlin) SDP (spray-dried powder) tablet formulation, 250mg orally once daily on days 1-5 of a 28 day cycle with enzalutamide orally 160mg once daily.

This was repeated every 28 days until progression.

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Idasanutlin  |
| Investigational medicinal product code | RO5503781    |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

RO5503781 (Idasanutlin) SDP (spray-dried powder) tablet formulation, 250mg orally once daily on days 1-5 of a 28 day cycle

|                                        |              |
|----------------------------------------|--------------|
| Investigational medicinal product name | Enzalutamide |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

enzalutamide 160mg once daily continuously

| <b>Number of subjects in period 1</b> | Cohort -1 | Cohort 1 | Cohort 1* |
|---------------------------------------|-----------|----------|-----------|
| Started                               | 3         | 3        | 3         |
| Completed                             | 3         | 3        | 3         |

| <b>Number of subjects in period 1</b> | Cohort 2 | Cohort 3B | Cohort 1E |
|---------------------------------------|----------|-----------|-----------|
| Started                               | 3        | 7         | 3         |
| Completed                             | 3        | 7         | 3         |

## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                                                                                                                                                                                           |           |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                     | Cohort -1 |
| Reporting group description:<br>RO5503781 (Idasanutlin) MBP (microprecipitated bulk powder) tablet formulation, a single dose given orally on day -7, then 200mg orally once daily on days 1-3 of a 28 day cycle with abiraterone orally 1000mg once daily and prednisolone orally 5mg twice a day.<br>This was repeated every 28 days until progression. |           |
| Reporting group title                                                                                                                                                                                                                                                                                                                                     | Cohort 1  |
| Reporting group description:<br>RO5503781 (Idasanutlin) MBP (microprecipitated bulk powder) tablet formulation, a single dose given orally on day -7, then 200mg orally once daily on days 1-5 of a 28 day cycle with abiraterone orally 1000mg once daily and prednisolone orally 5mg twice a day.<br>This was repeated every 28 days until progression. |           |
| Reporting group title                                                                                                                                                                                                                                                                                                                                     | Cohort 1* |
| Reporting group description:<br>RO5503781 (Idasanutlin) MBP (microprecipitated bulk powder) tablet formulation 200mg orally once daily on days 1-5 of a 28 day cycle with abiraterone orally 1000mg once daily and prednisolone orally 5mg twice a day.<br>This was repeated every 28 days until progression.                                             |           |
| Reporting group title                                                                                                                                                                                                                                                                                                                                     | Cohort 2  |
| Reporting group description:<br>RO5503781 (Idasanutlin) MBP (microprecipitated bulk powder) tablet formulation, 400mg orally once daily on days 1-5 of a 28 day cycle with abiraterone orally 1000mg once daily and prednisolone orally 5mg twice a day.<br>This was repeated every 28 days until progression.                                            |           |
| Reporting group title                                                                                                                                                                                                                                                                                                                                     | Cohort 3B |
| Reporting group description:<br>RO5503781 (Idasanutlin) SDP (spray-dried powder) tablet formulation, 250mg orally once daily on days 1-5 of a 28 day cycle with abiraterone orally 1000mg once daily and prednisolone orally 5mg twice a day.<br>This was repeated every 28 days until progression.                                                       |           |
| Reporting group title                                                                                                                                                                                                                                                                                                                                     | Cohort 1E |
| Reporting group description:<br>RO5503781 (Idasanutlin) SDP (spray-dried powder) tablet formulation, 250mg orally once daily on days 1-5 of a 28 day cycle with enzalutamide orally 160mg once daily.<br>This was repeated every 28 days until progression.                                                                                               |           |

| Reporting group values                             | Cohort -1 | Cohort 1 | Cohort 1* |
|----------------------------------------------------|-----------|----------|-----------|
| Number of subjects                                 | 3         | 3        | 3         |
| Age categorical                                    |           |          |           |
| Units: Subjects                                    |           |          |           |
| In utero                                           | 0         | 0        | 0         |
| Preterm newborn infants (gestational age < 37 wks) | 0         | 0        | 0         |
| Newborns (0-27 days)                               | 0         | 0        | 0         |
| Infants and toddlers (28 days-23 months)           | 0         | 0        | 0         |
| Children (2-11 years)                              | 0         | 0        | 0         |
| Adolescents (12-17 years)                          | 0         | 0        | 0         |
| Adults (18-64 years)                               | 1         | 3        | 2         |
| From 65-84 years                                   | 2         | 0        | 1         |
| 85 years and over                                  | 0         | 0        | 0         |



|                    |   |   |   |
|--------------------|---|---|---|
| Gender categorical |   |   |   |
| Units: Subjects    |   |   |   |
| Female             | 0 | 0 | 0 |
| Male               | 3 | 3 | 3 |

| Reporting group values                             | Cohort 2 | Cohort 3B | Cohort 1E |
|----------------------------------------------------|----------|-----------|-----------|
| Number of subjects                                 | 3        | 7         | 3         |
| Age categorical                                    |          |           |           |
| Units: Subjects                                    |          |           |           |
| In utero                                           | 0        | 0         | 0         |
| Preterm newborn infants (gestational age < 37 wks) | 0        | 0         | 0         |
| Newborns (0-27 days)                               | 0        | 0         | 0         |
| Infants and toddlers (28 days-23 months)           | 0        | 0         | 0         |
| Children (2-11 years)                              | 0        | 0         | 0         |
| Adolescents (12-17 years)                          | 0        | 0         | 0         |
| Adults (18-64 years)                               | 3        | 4         | 3         |
| From 65-84 years                                   | 0        | 3         | 0         |
| 85 years and over                                  | 0        | 0         | 0         |
| Gender categorical                                 |          |           |           |
| Units: Subjects                                    |          |           |           |
| Female                                             | 0        | 0         | 0         |
| Male                                               | 3        | 7         | 3         |

| Reporting group values                             | Total |  |  |
|----------------------------------------------------|-------|--|--|
| Number of subjects                                 | 22    |  |  |
| Age categorical                                    |       |  |  |
| Units: Subjects                                    |       |  |  |
| In utero                                           | 0     |  |  |
| Preterm newborn infants (gestational age < 37 wks) | 0     |  |  |
| Newborns (0-27 days)                               | 0     |  |  |
| Infants and toddlers (28 days-23 months)           | 0     |  |  |
| Children (2-11 years)                              | 0     |  |  |
| Adolescents (12-17 years)                          | 0     |  |  |
| Adults (18-64 years)                               | 16    |  |  |
| From 65-84 years                                   | 6     |  |  |
| 85 years and over                                  | 0     |  |  |
| Gender categorical                                 |       |  |  |
| Units: Subjects                                    |       |  |  |
| Female                                             | 0     |  |  |
| Male                                               | 22    |  |  |

### Subject analysis sets

|                                                            |                                    |
|------------------------------------------------------------|------------------------------------|
| Subject analysis set title                                 | Phase I Safety Population          |
| Subject analysis set type                                  | Safety analysis                    |
| Subject analysis set description:                          |                                    |
| Phase I patients with one or more dose of study medication |                                    |
| Subject analysis set title                                 | Phase I Evaluable Study Population |

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

- Any patient who has experienced a DLT
- Any patient who has received 5 consecutive days of treatment with RO5503781 within the first 21 days of combination therapy
- Any patient who has received at least 80% of planned doses of abiraterone or enzalutamide within the first 21 days of combination therapy

Any patient who has dose modifications not permitted by study protocol within the first 21 days will NOT be evaluable unless they experience a DLT

| Reporting group values                                | Phase I Safety Population | Phase I Evaluable Study Population |  |
|-------------------------------------------------------|---------------------------|------------------------------------|--|
| Number of subjects                                    | 22                        | 21                                 |  |
| Age categorical<br>Units: Subjects                    |                           |                                    |  |
| In utero                                              | 0                         | 0                                  |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0                         | 0                                  |  |
| Newborns (0-27 days)                                  | 0                         | 0                                  |  |
| Infants and toddlers (28 days-23 months)              | 0                         | 0                                  |  |
| Children (2-11 years)                                 | 0                         | 0                                  |  |
| Adolescents (12-17 years)                             | 0                         | 0                                  |  |
| Adults (18-64 years)                                  | 16                        | 15                                 |  |
| From 65-84 years                                      | 6                         | 6                                  |  |
| 85 years and over                                     | 0                         | 0                                  |  |
| Gender categorical<br>Units: Subjects                 |                           |                                    |  |
| Female                                                | 0                         | 0                                  |  |
| Male                                                  | 22                        | 21                                 |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                               |                                    |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                         | Cohort -1                          |
| Reporting group description:<br>RO5503781 (Idasanutlin) MBP (microprecipitated bulk powder) tablet formulation, a single dose given orally on day -7, then 200mg orally once daily on days 1-3 of a 28 day cycle with abiraterone orally 1000mg once daily and prednisolone orally 5mg twice a day.<br>This was repeated every 28 days until progression.                                                     |                                    |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                         | Cohort 1                           |
| Reporting group description:<br>RO5503781 (Idasanutlin) MBP (microprecipitated bulk powder) tablet formulation, a single dose given orally on day -7, then 200mg orally once daily on days 1-5 of a 28 day cycle with abiraterone orally 1000mg once daily and prednisolone orally 5mg twice a day.<br>This was repeated every 28 days until progression.                                                     |                                    |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                         | Cohort 1*                          |
| Reporting group description:<br>RO5503781 (Idasanutlin) MBP (microprecipitated bulk powder) tablet formulation 200mg orally once daily on days 1-5 of a 28 day cycle with abiraterone orally 1000mg once daily and prednisolone orally 5mg twice a day.<br>This was repeated every 28 days until progression.                                                                                                 |                                    |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                         | Cohort 2                           |
| Reporting group description:<br>RO5503781 (Idasanutlin) MBP (microprecipitated bulk powder) tablet formulation, 400mg orally once daily on days 1-5 of a 28 day cycle with abiraterone orally 1000mg once daily and prednisolone orally 5mg twice a day.<br>This was repeated every 28 days until progression.                                                                                                |                                    |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                         | Cohort 3B                          |
| Reporting group description:<br>RO5503781 (Idasanutlin) SDP (spray-dried powder) tablet formulation, 250mg orally once daily on days 1-5 of a 28 day cycle with abiraterone orally 1000mg once daily and prednisolone orally 5mg twice a day.<br>This was repeated every 28 days until progression.                                                                                                           |                                    |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                         | Cohort 1E                          |
| Reporting group description:<br>RO5503781 (Idasanutlin) SDP (spray-dried powder) tablet formulation, 250mg orally once daily on days 1-5 of a 28 day cycle with enzalutamide orally 160mg once daily.<br>This was repeated every 28 days until progression.                                                                                                                                                   |                                    |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                    | Phase I Safety Population          |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                     | Safety analysis                    |
| Subject analysis set description:<br>Phase I patients with one or more dose of study medication                                                                                                                                                                                                                                                                                                               |                                    |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                    | Phase I Evaluable Study Population |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                     | Full analysis                      |
| Subject analysis set description: <ul style="list-style-type: none"><li>Any patient who has experienced a DLT</li><li>Any patient who has received 5 consecutive days of treatment with RO5503781 within the first 21 days of combination therapy</li><li>Any patient who has received at least 80% of planned doses of abiraterone or enzalutamide within the first 21 days of combination therapy</li></ul> |                                    |
| Any patient who has dose modifications not permitted by study protocol within the first 21 days will NOT be evaluable unless they experience a DLT                                                                                                                                                                                                                                                            |                                    |

## Primary: Incidence of dose-limiting toxicities

|                 |                                                      |
|-----------------|------------------------------------------------------|
| End point title | Incidence of dose-limiting toxicities <sup>[1]</sup> |
|-----------------|------------------------------------------------------|

End point description:

Any of the following events beginning between the first administration of RO and 21 days after starting combination therapy if, in the opinion of the investigator, the event is due to the combination of abiraterone/enzalutamide, RO and prednisolone (if applicable) will be considered a dose limiting toxicity (DLT):

- \* Grade 4 neutropenia  $\geq 7$  days duration
- \* Grade 3–4 neutropenia associated with an oral temperature  $\geq 38.5^{\circ}\text{C}$
- \* Grade 3–4 neutropenia associated with bacteriologically proven sepsis
- \* Any grade 4 thrombocytopenia
- \* Grade 3 thrombocytopenia associated with non-traumatic bleeding (except where this can be explained by therapeutic anticoagulation)
- \* Any other clinically significant grade 3 or above toxicity except suboptimally-treated nausea or vomiting

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

End point timeframe:

Between the first administration of RO and 21 days after starting combination therapy

Notes:

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

Justification: The Phase I part of the trial was to determine the maximum tolerated dose based on descriptive data only and not statistical analysis

| End point values            | Cohort -1       | Cohort 1        | Cohort 1*       | Cohort 2        |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type          | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3               | 3               | 3               | 3               |
| Units: Patients             | 0               | 0               | 0               | 0               |

| End point values            | Cohort 3B       | Cohort 1E       | Phase I<br>Evaluable<br>Study<br>Population |  |
|-----------------------------|-----------------|-----------------|---------------------------------------------|--|
| Subject group type          | Reporting group | Reporting group | Subject analysis set                        |  |
| Number of subjects analysed | 6               | 3               | 21                                          |  |
| Units: Patients             | 1               | 0               | 1                                           |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From consent until resolution, or for at least 30 days after discontinuation of study medication, whichever comes first or until toxicity has resolved to baseline or < Grade 1, or until the toxicity is considered to be irreversible.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 19.0   |

### Reporting groups

|                                |           |
|--------------------------------|-----------|
| Reporting group title          | Cohort -1 |
| Reporting group description: - |           |
| Reporting group title          | Cohort 1  |
| Reporting group description: - |           |
| Reporting group title          | Cohort 1* |
| Reporting group description: - |           |
| Reporting group title          | Cohort 1E |
| Reporting group description: - |           |
| Reporting group title          | Cohort 2  |
| Reporting group description: - |           |
| Reporting group title          | Cohort 3B |
| Reporting group description: - |           |

| Serious adverse events                                                               | Cohort -1                                                                                                    | Cohort 1       | Cohort 1*      |
|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|----------------|----------------|
| Total subjects affected by serious adverse events                                    |                                                                                                              |                |                |
| subjects affected / exposed                                                          | 3 / 3 (100.00%)                                                                                              | 2 / 3 (66.67%) | 2 / 3 (66.67%) |
| number of deaths (all causes)                                                        | 1                                                                                                            | 0              | 0              |
| number of deaths resulting from adverse events                                       | 0                                                                                                            | 0              | 0              |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps)                  |                                                                                                              |                |                |
| MYELODYSPLASTIC SYNDROME                                                             | Additional description: MYELODYSPLASTIC SYNDROME                                                             |                |                |
| alternative assessment type: Non-systematic                                          |                                                                                                              |                |                |
| subjects affected / exposed                                                          | 0 / 3 (0.00%)                                                                                                | 0 / 3 (0.00%)  | 0 / 3 (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          |
| NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - OTHER, SPECIFY | Additional description: NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - OTHER, SPECIFY |                |                |
| alternative assessment type: Non-systematic                                          |                                                                                                              |                |                |

|                                                      |                                                                          |                |                |
|------------------------------------------------------|--------------------------------------------------------------------------|----------------|----------------|
| subjects affected / exposed                          | 1 / 3 (33.33%)                                                           | 0 / 3 (0.00%)  | 0 / 3 (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          |
| TUMOR PAIN                                           | Additional description: TUMOR PAIN                                       |                |                |
| alternative assessment type: Non-systematic          |                                                                          |                |                |
| subjects affected / exposed                          | 0 / 3 (0.00%)                                                            | 1 / 3 (33.33%) | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all      | 0 / 0                                                                    | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0                                                                    | 0 / 0          | 0 / 0          |
| Vascular disorders                                   |                                                                          |                |                |
| THROMBOEMBOLIC EVENT                                 | Additional description: THROMBOEMBOLIC EVENT                             |                |                |
| alternative assessment type: Non-systematic          |                                                                          |                |                |
| subjects affected / exposed                          | 0 / 3 (0.00%)                                                            | 1 / 3 (33.33%) | 1 / 3 (33.33%) |
| occurrences causally related to treatment / all      | 0 / 0                                                                    | 1 / 1          | 2 / 2          |
| deaths causally related to treatment / all           | 0 / 0                                                                    | 0 / 0          | 0 / 0          |
| Surgical and medical procedures                      |                                                                          |                |                |
| SURGICAL AND MEDICAL PROCEDURES - OTHER, SPECIFY     | Additional description: SURGICAL AND MEDICAL PROCEDURES - OTHER, SPECIFY |                |                |
| alternative assessment type: Non-systematic          |                                                                          |                |                |
| subjects affected / exposed                          | 1 / 3 (33.33%)                                                           | 0 / 3 (0.00%)  | 0 / 3 (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          |
| General disorders and administration site conditions |                                                                          |                |                |
| EDEMA LIMBS                                          | Additional description: EDEMA LIMBS                                      |                |                |
| alternative assessment type: Non-systematic          |                                                                          |                |                |
| subjects affected / exposed                          | 1 / 3 (33.33%)                                                           | 0 / 3 (0.00%)  | 0 / 3 (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          |
| PAIN                                                 | Additional description: PAIN                                             |                |                |
| alternative assessment type: Non-systematic          |                                                                          |                |                |
| subjects affected / exposed                          | 0 / 3 (0.00%)                                                            | 1 / 3 (33.33%) | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all      | 0 / 0                                                                    | 0 / 2          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0                                                                    | 0 / 0          | 0 / 0          |
| Reproductive system and breast disorders             |                                                                          |                |                |

|                                                                                                                                                                                                                                                    |                                                         |                |                |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|----------------|----------------|
| GENITAL EDEMA<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                                       | Additional description: GENITAL EDEMA                   |                |                |
|                                                                                                                                                                                                                                                    | 1 / 3 (33.33%)                                          | 0 / 3 (0.00%)  | 0 / 3 (0.00%)  |
|                                                                                                                                                                                                                                                    | 0 / 1                                                   | 0 / 0          | 0 / 0          |
|                                                                                                                                                                                                                                                    | 0 / 0                                                   | 0 / 0          | 0 / 0          |
|                                                                                                                                                                                                                                                    |                                                         |                |                |
| Respiratory, thoracic and mediastinal disorders<br>PRODUCTIVE COUGH<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | Additional description: PRODUCTIVE COUGH                |                |                |
|                                                                                                                                                                                                                                                    | 0 / 3 (0.00%)                                           | 1 / 3 (33.33%) | 0 / 3 (0.00%)  |
|                                                                                                                                                                                                                                                    | 0 / 0                                                   | 0 / 1          | 0 / 0          |
|                                                                                                                                                                                                                                                    | 0 / 0                                                   | 0 / 0          | 0 / 0          |
|                                                                                                                                                                                                                                                    |                                                         |                |                |
| Psychiatric disorders<br>DEPRESSION<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                 | Additional description: DEPRESSION                      |                |                |
|                                                                                                                                                                                                                                                    | 1 / 3 (33.33%)                                          | 0 / 3 (0.00%)  | 0 / 3 (0.00%)  |
|                                                                                                                                                                                                                                                    | 1 / 1                                                   | 0 / 0          | 0 / 0          |
|                                                                                                                                                                                                                                                    | 0 / 0                                                   | 0 / 0          | 0 / 0          |
|                                                                                                                                                                                                                                                    |                                                         |                |                |
| Investigations<br>CREATININE INCREASED<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                              | Additional description: CREATININE INCREASED            |                |                |
|                                                                                                                                                                                                                                                    | 0 / 3 (0.00%)                                           | 0 / 3 (0.00%)  | 0 / 3 (0.00%)  |
|                                                                                                                                                                                                                                                    | 0 / 0                                                   | 0 / 0          | 0 / 0          |
|                                                                                                                                                                                                                                                    | 0 / 0                                                   | 0 / 0          | 0 / 0          |
|                                                                                                                                                                                                                                                    |                                                         |                |                |
| INVESTIGATIONS - OTHER, SPECIFY<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                     | Additional description: INVESTIGATIONS - OTHER, SPECIFY |                |                |
|                                                                                                                                                                                                                                                    | 1 / 3 (33.33%)                                          | 0 / 3 (0.00%)  | 0 / 3 (0.00%)  |
|                                                                                                                                                                                                                                                    | 0 / 1                                                   | 0 / 0          | 0 / 0          |
|                                                                                                                                                                                                                                                    | 0 / 0                                                   | 0 / 0          | 0 / 0          |
|                                                                                                                                                                                                                                                    |                                                         |                |                |
| PLATELET COUNT DECREASED<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                            | Additional description: PLATELET COUNT DECREASED        |                |                |
|                                                                                                                                                                                                                                                    | 0 / 3 (0.00%)                                           | 1 / 3 (33.33%) | 1 / 3 (33.33%) |
|                                                                                                                                                                                                                                                    | 0 / 0                                                   | 1 / 1          | 1 / 1          |
|                                                                                                                                                                                                                                                    | 0 / 0                                                   | 0 / 0          | 0 / 0          |
|                                                                                                                                                                                                                                                    |                                                         |                |                |
| Cardiac disorders                                                                                                                                                                                                                                  |                                                         |                |                |

|                                                                                                                                                                                                                                                     |                                                    |                |                |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|----------------|----------------|
| <b>ATRIAL FIBRILLATION</b><br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                           | Additional description: ATRIAL FIBRILLATION        |                |                |
|                                                                                                                                                                                                                                                     | 1 / 3 (33.33%)                                     | 0 / 3 (0.00%)  | 0 / 3 (0.00%)  |
|                                                                                                                                                                                                                                                     | 1 / 1                                              | 0 / 0          | 0 / 0          |
|                                                                                                                                                                                                                                                     | 0 / 0                                              | 0 / 0          | 0 / 0          |
| <b>MYOCARDIAL INFARCTION</b><br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                         | Additional description: MYOCARDIAL INFARCTION      |                |                |
|                                                                                                                                                                                                                                                     | 0 / 3 (0.00%)                                      | 1 / 3 (33.33%) | 1 / 3 (33.33%) |
|                                                                                                                                                                                                                                                     | 0 / 0                                              | 1 / 1          | 0 / 1          |
|                                                                                                                                                                                                                                                     | 0 / 0                                              | 0 / 0          | 0 / 0          |
| <b>Nervous system disorders</b><br><b>TRANSIENT ISCHEMIC ATTACKS</b><br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | Additional description: TRANSIENT ISCHEMIC ATTACKS |                |                |
|                                                                                                                                                                                                                                                     | 0 / 3 (0.00%)                                      | 1 / 3 (33.33%) | 0 / 3 (0.00%)  |
|                                                                                                                                                                                                                                                     | 0 / 0                                              | 0 / 1          | 0 / 0          |
|                                                                                                                                                                                                                                                     | 0 / 0                                              | 0 / 0          | 0 / 0          |
| <b>Blood and lymphatic system disorders</b><br><b>ANEMIA</b><br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all         | Additional description: ANEMIA                     |                |                |
|                                                                                                                                                                                                                                                     | 0 / 3 (0.00%)                                      | 0 / 3 (0.00%)  | 0 / 3 (0.00%)  |
|                                                                                                                                                                                                                                                     | 0 / 0                                              | 0 / 0          | 0 / 0          |
|                                                                                                                                                                                                                                                     | 0 / 0                                              | 0 / 0          | 0 / 0          |
| <b>Gastrointestinal disorders</b><br><b>COLITIS</b><br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                  | Additional description: COLITIS                    |                |                |
|                                                                                                                                                                                                                                                     | 0 / 3 (0.00%)                                      | 0 / 3 (0.00%)  | 1 / 3 (33.33%) |
|                                                                                                                                                                                                                                                     | 0 / 0                                              | 0 / 0          | 0 / 1          |
|                                                                                                                                                                                                                                                     | 0 / 0                                              | 0 / 0          | 0 / 0          |
| <b>COLONIC OBSTRUCTION</b><br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                           | Additional description: COLONIC OBSTRUCTION        |                |                |
|                                                                                                                                                                                                                                                     | 0 / 3 (0.00%)                                      | 0 / 3 (0.00%)  | 0 / 3 (0.00%)  |
|                                                                                                                                                                                                                                                     | 0 / 0                                              | 0 / 0          | 0 / 0          |
|                                                                                                                                                                                                                                                     | 0 / 0                                              | 0 / 0          | 0 / 0          |
| <b>DIARRHEA</b><br>                                                                                                                                                                                                                                 | Additional description: DIARRHEA                   |                |                |
|                                                                                                                                                                                                                                                     |                                                    |                |                |
|                                                                                                                                                                                                                                                     |                                                    |                |                |
|                                                                                                                                                                                                                                                     |                                                    |                |                |



|                                                 |                                             |                |                |
|-------------------------------------------------|---------------------------------------------|----------------|----------------|
| alternative assessment type: Non-systematic     |                                             |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)                               | 0 / 3 (0.00%)  | 1 / 3 (33.33%) |
| occurrences causally related to treatment / all | 0 / 0                                       | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0                                       | 0 / 0          | 0 / 0          |
| NAUSEA                                          | Additional description: NAUSEA              |                |                |
| alternative assessment type: Non-systematic     |                                             |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)                               | 0 / 3 (0.00%)  | 0 / 3 (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                                        | Additional description: VOMITING            |                |                |
| alternative assessment type: Non-systematic     |                                             |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)                               | 0 / 3 (0.00%)  | 1 / 3 (33.33%) |
| occurrences causally related to treatment / all | 0 / 0                                       | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0                                       | 0 / 0          | 0 / 0          |
| Renal and urinary disorders                     |                                             |                |                |
| HEMATURIA                                       | Additional description: HEMATURIA           |                |                |
| alternative assessment type: Non-systematic     |                                             |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)                               | 1 / 3 (33.33%) | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0                                       | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0                                       | 0 / 0          | 0 / 0          |
| URINARY RETENTION                               | Additional description: URINARY RETENTION   |                |                |
| alternative assessment type: Non-systematic     |                                             |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)                               | 1 / 3 (33.33%) | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0                                       | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0                                       | 0 / 0          | 0 / 0          |
| Musculoskeletal and connective tissue disorders |                                             |                |                |
| BACK PAIN                                       | Additional description: BACK PAIN           |                |                |
| alternative assessment type: Non-systematic     |                                             |                |                |
| subjects affected / exposed                     | 1 / 3 (33.33%)                              | 0 / 3 (0.00%)  | 0 / 3 (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          |
| Infections and infestations                     |                                             |                |                |
| BRONCHIAL INFECTION                             | Additional description: BRONCHIAL INFECTION |                |                |

|                                                 |                                                 |                |                |
|-------------------------------------------------|-------------------------------------------------|----------------|----------------|
| alternative assessment type: Non-systematic     |                                                 |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)                                   | 0 / 3 (0.00%)  | 0 / 3 (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          |
| LUNG INFECTION                                  | Additional description: LUNG INFECTION          |                |                |
| alternative assessment type: Non-systematic     |                                                 |                |                |
| subjects affected / exposed                     | 1 / 3 (33.33%)                                  | 1 / 3 (33.33%) | 1 / 3 (33.33%) |
| occurrences causally related to treatment / all | 0 / 1                                           | 0 / 1          | 2 / 2          |
| deaths causally related to treatment / all      | 0 / 0                                           | 0 / 0          | 0 / 0          |
| URINARY TRACT INFECTION                         | Additional description: URINARY TRACT INFECTION |                |                |
| alternative assessment type: Non-systematic     |                                                 |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)                                   | 0 / 3 (0.00%)  | 1 / 3 (33.33%) |
| occurrences causally related to treatment / all | 0 / 0                                           | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0                                           | 0 / 0          | 0 / 0          |
| Metabolism and nutrition disorders              |                                                 |                |                |
| HYPERCALCEMIA                                   | Additional description: HYPERCALCEMIA           |                |                |
| alternative assessment type: Non-systematic     |                                                 |                |                |
| subjects affected / exposed                     | 1 / 3 (33.33%)                                  | 0 / 3 (0.00%)  | 0 / 3 (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          |
| HYPERGLYCEMIA                                   | Additional description: HYPERGLYCEMIA           |                |                |
| alternative assessment type: Non-systematic     |                                                 |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)                                   | 0 / 3 (0.00%)  | 0 / 3 (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          |
| HYPOKALEMIA                                     | Additional description: HYPOKALEMIA             |                |                |
| alternative assessment type: Non-systematic     |                                                 |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)                                   | 0 / 3 (0.00%)  | 0 / 3 (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          |
| HYPOPHOSPHATEMIA                                | Additional description: HYPOPHOSPHATEMIA        |                |                |
| alternative assessment type: Non-systematic     |                                                 |                |                |

|                                                 |               |               |               |
|-------------------------------------------------|---------------|---------------|---------------|
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (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         |

| Serious adverse events                                                               | Cohort 1E                                                                                                    | Cohort 2       | Cohort 3B      |
|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|----------------|----------------|
| Total subjects affected by serious adverse events                                    |                                                                                                              |                |                |
| subjects affected / exposed                                                          | 1 / 3 (33.33%)                                                                                               | 1 / 3 (33.33%) | 6 / 7 (85.71%) |
| number of deaths (all causes)                                                        | 0                                                                                                            | 0              | 0              |
| number of deaths resulting from adverse events                                       | 0                                                                                                            | 0              | 0              |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps)                  |                                                                                                              |                |                |
| MYELODYSPLASTIC SYNDROME                                                             | Additional description: MYELODYSPLASTIC SYNDROME                                                             |                |                |
| alternative assessment type: Non-systematic                                          |                                                                                                              |                |                |
| subjects affected / exposed                                                          | 0 / 3 (0.00%)                                                                                                | 0 / 3 (0.00%)  | 1 / 7 (14.29%) |
| occurrences causally related to treatment / all                                      | 0 / 0                                                                                                        | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all                                           | 0 / 0                                                                                                        | 0 / 0          | 0 / 0          |
| NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - OTHER, SPECIFY | Additional description: NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - OTHER, SPECIFY |                |                |
| alternative assessment type: Non-systematic                                          |                                                                                                              |                |                |
| subjects affected / exposed                                                          | 0 / 3 (0.00%)                                                                                                | 1 / 3 (33.33%) | 1 / 7 (14.29%) |
| occurrences causally related to treatment / all                                      | 0 / 0                                                                                                        | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all                                           | 0 / 0                                                                                                        | 0 / 0          | 0 / 0          |
| TUMOR PAIN                                                                           | Additional description: TUMOR PAIN                                                                           |                |                |
| alternative assessment type: Non-systematic                                          |                                                                                                              |                |                |
| subjects affected / exposed                                                          | 0 / 3 (0.00%)                                                                                                | 0 / 3 (0.00%)  | 0 / 7 (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          |
| Vascular disorders                                                                   |                                                                                                              |                |                |
| THROMBOEMBOLIC EVENT                                                                 | Additional description: THROMBOEMBOLIC EVENT                                                                 |                |                |
| alternative assessment type: Non-systematic                                          |                                                                                                              |                |                |
| subjects affected / exposed                                                          | 0 / 3 (0.00%)                                                                                                | 0 / 3 (0.00%)  | 0 / 7 (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          |
| Surgical and medical procedures                                                      |                                                                                                              |                |                |
| SURGICAL AND MEDICAL PROCEDURES - OTHER, SPECIFY                                     | Additional description: SURGICAL AND MEDICAL PROCEDURES - OTHER, SPECIFY                                     |                |                |

|                                                      |                                          |               |                |
|------------------------------------------------------|------------------------------------------|---------------|----------------|
| alternative assessment type: Non-systematic          |                                          |               |                |
| subjects affected / exposed                          | 0 / 3 (0.00%)                            | 0 / 3 (0.00%) | 1 / 7 (14.29%) |
| occurrences causally related to treatment / all      | 0 / 0                                    | 0 / 0         | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0                                    | 0 / 0         | 0 / 0          |
| General disorders and administration site conditions |                                          |               |                |
| EDEMA LIMBS                                          | Additional description: EDEMA LIMBS      |               |                |
| alternative assessment type: Non-systematic          |                                          |               |                |
| subjects affected / exposed                          | 0 / 3 (0.00%)                            | 0 / 3 (0.00%) | 0 / 7 (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          |
| PAIN                                                 | Additional description: PAIN             |               |                |
| alternative assessment type: Non-systematic          |                                          |               |                |
| subjects affected / exposed                          | 0 / 3 (0.00%)                            | 0 / 3 (0.00%) | 1 / 7 (14.29%) |
| occurrences causally related to treatment / all      | 0 / 0                                    | 0 / 0         | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0                                    | 0 / 0         | 0 / 0          |
| Reproductive system and breast disorders             |                                          |               |                |
| GENITAL EDEMA                                        | Additional description: GENITAL EDEMA    |               |                |
| alternative assessment type: Non-systematic          |                                          |               |                |
| subjects affected / exposed                          | 0 / 3 (0.00%)                            | 0 / 3 (0.00%) | 0 / 7 (0.00%)  |
| occurrences causally related to treatment / all      | 0 / 0                                    | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0                                    | 0 / 0         | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders      |                                          |               |                |
| PRODUCTIVE COUGH                                     | Additional description: PRODUCTIVE COUGH |               |                |
| alternative assessment type: Non-systematic          |                                          |               |                |
| subjects affected / exposed                          | 0 / 3 (0.00%)                            | 0 / 3 (0.00%) | 0 / 7 (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          |
| Psychiatric disorders                                |                                          |               |                |
| DEPRESSION                                           | Additional description: DEPRESSION       |               |                |
| alternative assessment type: Non-systematic          |                                          |               |                |
| subjects affected / exposed                          | 0 / 3 (0.00%)                            | 0 / 3 (0.00%) | 0 / 7 (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          |

|                                                 |                                                         |               |                |
|-------------------------------------------------|---------------------------------------------------------|---------------|----------------|
| Investigations                                  |                                                         |               |                |
| CREATININE INCREASED                            | Additional description: CREATININE INCREASED            |               |                |
| alternative assessment type: Non-systematic     |                                                         |               |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)                                           | 0 / 3 (0.00%) | 1 / 7 (14.29%) |
| occurrences causally related to treatment / all | 0 / 0                                                   | 0 / 0         | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0                                                   | 0 / 0         | 0 / 0          |
| INVESTIGATIONS - OTHER, SPECIFY                 | Additional description: INVESTIGATIONS - OTHER, SPECIFY |               |                |
| alternative assessment type: Non-systematic     |                                                         |               |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)                                           | 0 / 3 (0.00%) | 1 / 7 (14.29%) |
| occurrences causally related to treatment / all | 0 / 0                                                   | 0 / 0         | 2 / 2          |
| deaths causally related to treatment / all      | 0 / 0                                                   | 0 / 0         | 0 / 0          |
| PLATELET COUNT DECREASED                        | Additional description: PLATELET COUNT DECREASED        |               |                |
| alternative assessment type: Non-systematic     |                                                         |               |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)                                           | 0 / 3 (0.00%) | 1 / 7 (14.29%) |
| occurrences causally related to treatment / all | 0 / 0                                                   | 0 / 0         | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0                                                   | 0 / 0         | 0 / 0          |
| Cardiac disorders                               |                                                         |               |                |
| ATRIAL FIBRILLATION                             | Additional description: ATRIAL FIBRILLATION             |               |                |
| alternative assessment type: Non-systematic     |                                                         |               |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)                                           | 0 / 3 (0.00%) | 0 / 7 (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          |
| MYOCARDIAL INFARCTION                           | Additional description: MYOCARDIAL INFARCTION           |               |                |
| alternative assessment type: Non-systematic     |                                                         |               |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)                                           | 0 / 3 (0.00%) | 0 / 7 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0                                                   | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0                                                   | 0 / 0         | 0 / 0          |
| Nervous system disorders                        |                                                         |               |                |
| TRANSIENT ISCHEMIC ATTACKS                      | Additional description: TRANSIENT ISCHEMIC ATTACKS      |               |                |
| alternative assessment type: Non-systematic     |                                                         |               |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)                                           | 0 / 3 (0.00%) | 0 / 7 (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          |
| Blood and lymphatic system disorders            |                                                         |               |                |

|                                                 |                                             |               |                |
|-------------------------------------------------|---------------------------------------------|---------------|----------------|
| ANEMIA                                          | Additional description: ANEMIA              |               |                |
| alternative assessment type: Non-systematic     |                                             |               |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)                               | 0 / 3 (0.00%) | 1 / 7 (14.29%) |
| occurrences causally related to treatment / all | 0 / 0                                       | 0 / 0         | 2 / 2          |
| deaths causally related to treatment / all      | 0 / 0                                       | 0 / 0         | 0 / 0          |
| Gastrointestinal disorders                      |                                             |               |                |
| COLITIS                                         | Additional description: COLITIS             |               |                |
| alternative assessment type: Non-systematic     |                                             |               |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)                               | 0 / 3 (0.00%) | 0 / 7 (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          |
| COLONIC OBSTRUCTION                             | Additional description: COLONIC OBSTRUCTION |               |                |
| alternative assessment type: Non-systematic     |                                             |               |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)                               | 0 / 3 (0.00%) | 1 / 7 (14.29%) |
| occurrences causally related to treatment / all | 0 / 0                                       | 0 / 0         | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0                                       | 0 / 0         | 0 / 0          |
| DIARRHEA                                        | Additional description: DIARRHEA            |               |                |
| alternative assessment type: Non-systematic     |                                             |               |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)                               | 0 / 3 (0.00%) | 2 / 7 (28.57%) |
| occurrences causally related to treatment / all | 0 / 0                                       | 0 / 0         | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0                                       | 0 / 0         | 0 / 0          |
| NAUSEA                                          | Additional description: NAUSEA              |               |                |
| alternative assessment type: Non-systematic     |                                             |               |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)                               | 0 / 3 (0.00%) | 1 / 7 (14.29%) |
| occurrences causally related to treatment / all | 0 / 0                                       | 0 / 0         | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0                                       | 0 / 0         | 0 / 0          |
| VOMITING                                        | Additional description: VOMITING            |               |                |
| alternative assessment type: Non-systematic     |                                             |               |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)                               | 0 / 3 (0.00%) | 2 / 7 (28.57%) |
| occurrences causally related to treatment / all | 0 / 0                                       | 0 / 0         | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0                                       | 0 / 0         | 0 / 0          |
| Renal and urinary disorders                     |                                             |               |                |
| HEMATURIA                                       | Additional description: HEMATURIA           |               |                |
| alternative assessment type: Non-systematic     |                                             |               |                |

|                                                 |                                                 |                |                |
|-------------------------------------------------|-------------------------------------------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 3 (0.00%)                                   | 0 / 3 (0.00%)  | 0 / 7 (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          |
| URINARY RETENTION                               | Additional description: URINARY RETENTION       |                |                |
| alternative assessment type: Non-systematic     |                                                 |                |                |
| subjects affected / exposed                     | 1 / 3 (33.33%)                                  | 0 / 3 (0.00%)  | 0 / 7 (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          |
| Musculoskeletal and connective tissue disorders |                                                 |                |                |
| BACK PAIN                                       | Additional description: BACK PAIN               |                |                |
| alternative assessment type: Non-systematic     |                                                 |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)                                   | 1 / 3 (33.33%) | 0 / 7 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0                                           | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0                                           | 0 / 0          | 0 / 0          |
| Infections and infestations                     |                                                 |                |                |
| BRONCHIAL INFECTION                             | Additional description: BRONCHIAL INFECTION     |                |                |
| alternative assessment type: Non-systematic     |                                                 |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)                                   | 0 / 3 (0.00%)  | 1 / 7 (14.29%) |
| occurrences causally related to treatment / all | 0 / 0                                           | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0                                           | 0 / 0          | 0 / 0          |
| LUNG INFECTION                                  | Additional description: LUNG INFECTION          |                |                |
| alternative assessment type: Non-systematic     |                                                 |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)                                   | 0 / 3 (0.00%)  | 0 / 7 (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          |
| URINARY TRACT INFECTION                         | Additional description: URINARY TRACT INFECTION |                |                |
| alternative assessment type: Non-systematic     |                                                 |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)                                   | 0 / 3 (0.00%)  | 0 / 7 (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          |
| Metabolism and nutrition disorders              |                                                 |                |                |
| HYPERCALCEMIA                                   | Additional description: HYPERCALCEMIA           |                |                |
| alternative assessment type: Non-systematic     |                                                 |                |                |

|                                                 |                                          |               |                |
|-------------------------------------------------|------------------------------------------|---------------|----------------|
| subjects affected / exposed                     | 0 / 3 (0.00%)                            | 0 / 3 (0.00%) | 0 / 7 (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          |
| <b>HYPERGLYCEMIA</b>                            | Additional description: HYPERGLYCEMIA    |               |                |
| alternative assessment type: Non-systematic     |                                          |               |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)                            | 0 / 3 (0.00%) | 1 / 7 (14.29%) |
| occurrences causally related to treatment / all | 0 / 0                                    | 0 / 0         | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0                                    | 0 / 0         | 0 / 0          |
| <b>HYPOKALEMIA</b>                              | Additional description: HYPOKALEMIA      |               |                |
| alternative assessment type: Non-systematic     |                                          |               |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)                            | 0 / 3 (0.00%) | 1 / 7 (14.29%) |
| occurrences causally related to treatment / all | 0 / 0                                    | 0 / 0         | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0                                    | 0 / 0         | 0 / 0          |
| <b>HYPOPHOSPHATEMIA</b>                         | Additional description: HYPOPHOSPHATEMIA |               |                |
| alternative assessment type: Non-systematic     |                                          |               |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)                            | 0 / 3 (0.00%) | 1 / 7 (14.29%) |
| occurrences causally related to treatment / all | 0 / 0                                    | 0 / 0         | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0                                    | 0 / 0         | 0 / 0          |

Frequency threshold for reporting non-serious adverse events: 0 %

| <b>Non-serious adverse events</b>                                                    | Cohort -1                                                                                                    | Cohort 1        | Cohort 1*       |
|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|-----------------|-----------------|
| Total subjects affected by non-serious adverse events                                |                                                                                                              |                 |                 |
| subjects affected / exposed                                                          | 3 / 3 (100.00%)                                                                                              | 3 / 3 (100.00%) | 3 / 3 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps)                  |                                                                                                              |                 |                 |
| NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - OTHER, SPECIFY | Additional description: NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - OTHER, SPECIFY |                 |                 |
| alternative assessment type: Non-systematic                                          |                                                                                                              |                 |                 |
| subjects affected / exposed                                                          | 0 / 3 (0.00%)                                                                                                | 0 / 3 (0.00%)   | 0 / 3 (0.00%)   |
| occurrences (all)                                                                    | 0                                                                                                            | 0               | 0               |
| Vascular disorders                                                                   |                                                                                                              |                 |                 |
| FLUSHING                                                                             | Additional description: FLUSHING                                                                             |                 |                 |
| alternative assessment type: Non-systematic                                          |                                                                                                              |                 |                 |



|                                                      |                                              |                |                |
|------------------------------------------------------|----------------------------------------------|----------------|----------------|
| subjects affected / exposed                          | 0 / 3 (0.00%)                                | 0 / 3 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)                                    | 0                                            | 0              | 0              |
| HOT FLASHES                                          | Additional description: HOT FLASHES          |                |                |
| alternative assessment type: Non-systematic          |                                              |                |                |
| subjects affected / exposed                          | 2 / 3 (66.67%)                               | 2 / 3 (66.67%) | 0 / 3 (0.00%)  |
| occurrences (all)                                    | 2                                            | 15             | 0              |
| HYPERTENSION                                         | Additional description: HYPERTENSION         |                |                |
| alternative assessment type: Non-systematic          |                                              |                |                |
| subjects affected / exposed                          | 0 / 3 (0.00%)                                | 1 / 3 (33.33%) | 1 / 3 (33.33%) |
| occurrences (all)                                    | 0                                            | 2              | 1              |
| HYPOTENSION                                          | Additional description: HYPOTENSION          |                |                |
| alternative assessment type: Non-systematic          |                                              |                |                |
| subjects affected / exposed                          | 0 / 3 (0.00%)                                | 0 / 3 (0.00%)  | 1 / 3 (33.33%) |
| occurrences (all)                                    | 0                                            | 0              | 1              |
| PHLEBITIS                                            | Additional description: PHLEBITIS            |                |                |
| alternative assessment type: Non-systematic          |                                              |                |                |
| subjects affected / exposed                          | 1 / 3 (33.33%)                               | 0 / 3 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)                                    | 3                                            | 0              | 0              |
| THROMBOEMBOLIC EVENT                                 | Additional description: THROMBOEMBOLIC EVENT |                |                |
| alternative assessment type: Non-systematic          |                                              |                |                |
| subjects affected / exposed                          | 0 / 3 (0.00%)                                | 0 / 3 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)                                    | 0                                            | 0              | 0              |
| General disorders and administration site conditions |                                              |                |                |
| EDEMA FACE                                           | Additional description: EDEMA FACE           |                |                |
| alternative assessment type: Non-systematic          |                                              |                |                |
| subjects affected / exposed                          | 0 / 3 (0.00%)                                | 0 / 3 (0.00%)  | 1 / 3 (33.33%) |
| occurrences (all)                                    | 0                                            | 0              | 1              |
| EDEMA LIMBS                                          | Additional description: EDEMA LIMBS          |                |                |
| alternative assessment type: Non-systematic          |                                              |                |                |
| subjects affected / exposed                          | 1 / 3 (33.33%)                               | 1 / 3 (33.33%) | 0 / 3 (0.00%)  |
| occurrences (all)                                    | 1                                            | 1              | 0              |
| FATIGUE                                              | Additional description: FATIGUE              |                |                |
| alternative assessment type: Non-systematic          |                                              |                |                |

|                                                                       |                                                                                               |                 |                 |
|-----------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-----------------|-----------------|
| subjects affected / exposed                                           | 0 / 3 (0.00%)                                                                                 | 3 / 3 (100.00%) | 3 / 3 (100.00%) |
| occurrences (all)                                                     | 0                                                                                             | 7               | 20              |
| FEVER                                                                 | Additional description: FEVER                                                                 |                 |                 |
| alternative assessment type: Non-systematic                           |                                                                                               |                 |                 |
| subjects affected / exposed                                           | 1 / 3 (33.33%)                                                                                | 0 / 3 (0.00%)   | 0 / 3 (0.00%)   |
| occurrences (all)                                                     | 1                                                                                             | 0               | 0               |
| FLU LIKE SYMPTOMS                                                     | Additional description: FLU LIKE SYMPTOMS                                                     |                 |                 |
| alternative assessment type: Non-systematic                           |                                                                                               |                 |                 |
| subjects affected / exposed                                           | 1 / 3 (33.33%)                                                                                | 0 / 3 (0.00%)   | 1 / 3 (33.33%)  |
| occurrences (all)                                                     | 1                                                                                             | 0               | 1               |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - OTHER, SPECIFY | Additional description: GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - OTHER, SPECIFY |                 |                 |
| alternative assessment type: Non-systematic                           |                                                                                               |                 |                 |
| subjects affected / exposed                                           | 2 / 3 (66.67%)                                                                                | 1 / 3 (33.33%)  | 1 / 3 (33.33%)  |
| occurrences (all)                                                     | 3                                                                                             | 1               | 1               |
| HYPOTHERMIA                                                           | Additional description: HYPOTHERMIA                                                           |                 |                 |
| alternative assessment type: Non-systematic                           |                                                                                               |                 |                 |
| subjects affected / exposed                                           | 0 / 3 (0.00%)                                                                                 | 0 / 3 (0.00%)   | 0 / 3 (0.00%)   |
| occurrences (all)                                                     | 0                                                                                             | 0               | 0               |
| MALAISE                                                               | Additional description: MALAISE                                                               |                 |                 |
| alternative assessment type: Non-systematic                           |                                                                                               |                 |                 |
| subjects affected / exposed                                           | 0 / 3 (0.00%)                                                                                 | 0 / 3 (0.00%)   | 0 / 3 (0.00%)   |
| occurrences (all)                                                     | 0                                                                                             | 0               | 0               |
| NON-CARDIAC CHEST PAIN                                                | Additional description: NON-CARDIAC CHEST PAIN                                                |                 |                 |
| alternative assessment type: Non-systematic                           |                                                                                               |                 |                 |
| subjects affected / exposed                                           | 0 / 3 (0.00%)                                                                                 | 0 / 3 (0.00%)   | 0 / 3 (0.00%)   |
| occurrences (all)                                                     | 0                                                                                             | 0               | 0               |
| PAIN                                                                  | Additional description: PAIN                                                                  |                 |                 |
| alternative assessment type: Non-systematic                           |                                                                                               |                 |                 |
| subjects affected / exposed                                           | 3 / 3 (100.00%)                                                                               | 2 / 3 (66.67%)  | 2 / 3 (66.67%)  |
| occurrences (all)                                                     | 5                                                                                             | 12              | 2               |
| Immune system disorders                                               |                                                                                               |                 |                 |
| ALLERGIC REACTION                                                     | Additional description: ALLERGIC REACTION                                                     |                 |                 |
| alternative assessment type: Non-systematic                           |                                                                                               |                 |                 |

|                                                                  |                                                                                          |                |                |
|------------------------------------------------------------------|------------------------------------------------------------------------------------------|----------------|----------------|
| subjects affected / exposed                                      | 0 / 3 (0.00%)                                                                            | 0 / 3 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)                                                | 0                                                                                        | 0              | 0              |
| Reproductive system and breast disorders                         |                                                                                          |                |                |
| GYNECOMASTIA                                                     | Additional description: GYNECOMASTIA                                                     |                |                |
| alternative assessment type: Non-systematic                      |                                                                                          |                |                |
| subjects affected / exposed                                      | 0 / 3 (0.00%)                                                                            | 0 / 3 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)                                                | 0                                                                                        | 0              | 0              |
| PELVIC PAIN                                                      | Additional description: PELVIC PAIN                                                      |                |                |
| alternative assessment type: Non-systematic                      |                                                                                          |                |                |
| subjects affected / exposed                                      | 0 / 3 (0.00%)                                                                            | 0 / 3 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)                                                | 0                                                                                        | 0              | 0              |
| REPRODUCTIVE SYSTEM AND BREAST DISORDERS - OTHER, SPECIFY        | Additional description: REPRODUCTIVE SYSTEM AND BREAST DISORDERS - OTHER, SPECIFY        |                |                |
| alternative assessment type: Non-systematic                      |                                                                                          |                |                |
| subjects affected / exposed                                      | 1 / 3 (33.33%)                                                                           | 0 / 3 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)                                                | 1                                                                                        | 0              | 0              |
| Respiratory, thoracic and mediastinal disorders                  |                                                                                          |                |                |
| COUGH                                                            | Additional description: COUGH                                                            |                |                |
| alternative assessment type: Non-systematic                      |                                                                                          |                |                |
| subjects affected / exposed                                      | 1 / 3 (33.33%)                                                                           | 0 / 3 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)                                                | 2                                                                                        | 0              | 0              |
| DYSPNEA                                                          | Additional description: DYSPNEA                                                          |                |                |
| alternative assessment type: Non-systematic                      |                                                                                          |                |                |
| subjects affected / exposed                                      | 0 / 3 (0.00%)                                                                            | 1 / 3 (33.33%) | 1 / 3 (33.33%) |
| occurrences (all)                                                | 0                                                                                        | 3              | 1              |
| EPISTAXIS                                                        | Additional description: EPISTAXIS                                                        |                |                |
| alternative assessment type: Non-systematic                      |                                                                                          |                |                |
| subjects affected / exposed                                      | 0 / 3 (0.00%)                                                                            | 0 / 3 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)                                                | 0                                                                                        | 0              | 0              |
| LARYNGEAL INFLAMMATION                                           | Additional description: LARYNGEAL INFLAMMATION                                           |                |                |
| alternative assessment type: Non-systematic                      |                                                                                          |                |                |
| subjects affected / exposed                                      | 0 / 3 (0.00%)                                                                            | 0 / 3 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)                                                | 0                                                                                        | 0              | 0              |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - OTHER, SPECIFY | Additional description: RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - OTHER, SPECIFY |                |                |

|                                                                                                                                      |                                                                         |               |                |
|--------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|---------------|----------------|
| <p><b>SPECIFY</b></p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | 1 / 3 (33.33%)                                                          | 0 / 3 (0.00%) | 0 / 3 (0.00%)  |
|                                                                                                                                      | 1                                                                       | 0             | 0              |
|                                                                                                                                      | Additional description: SLEEP APNEA                                     |               |                |
|                                                                                                                                      | 0 / 3 (0.00%)                                                           | 0 / 3 (0.00%) | 0 / 3 (0.00%)  |
|                                                                                                                                      | 0                                                                       | 0             | 0              |
|                                                                                                                                      | Additional description: WHEEZING                                        |               |                |
|                                                                                                                                      | 1 / 3 (33.33%)                                                          | 0 / 3 (0.00%) | 0 / 3 (0.00%)  |
|                                                                                                                                      | 1                                                                       | 0             | 0              |
|                                                                                                                                      |                                                                         |               |                |
| Psychiatric disorders                                                                                                                |                                                                         |               |                |
| <b>ANXIETY</b>                                                                                                                       | Additional description: ANXIETY                                         |               |                |
| alternative assessment type: Non-systematic                                                                                          |                                                                         |               |                |
| subjects affected / exposed                                                                                                          | 0 / 3 (0.00%)                                                           | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all)                                                                                                                    | 0                                                                       | 0             | 1              |
| <b>CONFUSION</b>                                                                                                                     | Additional description: CONFUSION                                       |               |                |
| alternative assessment type: Non-systematic                                                                                          |                                                                         |               |                |
| subjects affected / exposed                                                                                                          | 0 / 3 (0.00%)                                                           | 0 / 3 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                                                                                                                    | 0                                                                       | 0             | 0              |
| <b>DEPRESSION</b>                                                                                                                    | Additional description: DEPRESSION                                      |               |                |
| alternative assessment type: Non-systematic                                                                                          |                                                                         |               |                |
| subjects affected / exposed                                                                                                          | 0 / 3 (0.00%)                                                           | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all)                                                                                                                    | 0                                                                       | 0             | 1              |
| <b>PSYCHIATRIC DISORDERS - OTHER, SPECIFY</b>                                                                                        | Additional description: PSYCHIATRIC DISORDERS - OTHER, SPECIFY          |               |                |
| alternative assessment type: Non-systematic                                                                                          |                                                                         |               |                |
| subjects affected / exposed                                                                                                          | 0 / 3 (0.00%)                                                           | 0 / 3 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                                                                                                                    | 0                                                                       | 0             | 0              |
| <b>Investigations</b>                                                                                                                |                                                                         |               |                |
| <b>ACTIVATED PARTIAL THROMBOPLASTIN TIME PROLONGED</b>                                                                               | Additional description: ACTIVATED PARTIAL THROMBOPLASTIN TIME PROLONGED |               |                |
| alternative assessment type: Non-systematic                                                                                          |                                                                         |               |                |
| subjects affected / exposed                                                                                                          | 0 / 3 (0.00%)                                                           | 0 / 3 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                                                                                                                    | 0                                                                       | 0             | 0              |

|                                                                                                                                                                                      |                                                         |                 |                |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|-----------------|----------------|
| <p>INVESTIGATIONS - OTHER, SPECIFY</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                | Additional description: INVESTIGATIONS - OTHER, SPECIFY |                 |                |
|                                                                                                                                                                                      | 0 / 3 (0.00%)                                           | 3 / 3 (100.00%) | 0 / 3 (0.00%)  |
|                                                                                                                                                                                      | 0                                                       | 4               | 0              |
|                                                                                                                                                                                      | Additional description: NEUTROPHIL COUNT DECREASED      |                 |                |
|                                                                                                                                                                                      | 0 / 3 (0.00%)                                           | 2 / 3 (66.67%)  | 0 / 3 (0.00%)  |
| <p>NEUTROPHIL COUNT DECREASED</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                     | 0                                                       | 2               | 0              |
|                                                                                                                                                                                      | Additional description: PLATELET COUNT DECREASED        |                 |                |
|                                                                                                                                                                                      | 0 / 3 (0.00%)                                           | 1 / 3 (33.33%)  | 0 / 3 (0.00%)  |
|                                                                                                                                                                                      | 0                                                       | 1               | 0              |
|                                                                                                                                                                                      | Additional description: WEIGHT GAIN                     |                 |                |
| <p>PLATELET COUNT DECREASED</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                       | 0 / 3 (0.00%)                                           | 0 / 3 (0.00%)   | 0 / 3 (0.00%)  |
|                                                                                                                                                                                      | 0                                                       | 0               | 0              |
|                                                                                                                                                                                      | Additional description: WEIGHT LOSS                     |                 |                |
|                                                                                                                                                                                      | 0 / 3 (0.00%)                                           | 0 / 3 (0.00%)   | 0 / 3 (0.00%)  |
|                                                                                                                                                                                      | 0                                                       | 0               | 0              |
| <p>WEIGHT GAIN</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                                    | Additional description: WEIGHT LOSS                     |                 |                |
|                                                                                                                                                                                      | 0 / 3 (0.00%)                                           | 0 / 3 (0.00%)   | 0 / 3 (0.00%)  |
|                                                                                                                                                                                      | 0                                                       | 0               | 0              |
|                                                                                                                                                                                      | Additional description: INJURY TO SUPERIOR VENA CAVA    |                 |                |
|                                                                                                                                                                                      |                                                         |                 |                |
| <p>Injury, poisoning and procedural complications</p> <p>BRUISING</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | Additional description: BRUISING                        |                 |                |
|                                                                                                                                                                                      | 1 / 3 (33.33%)                                          | 2 / 3 (66.67%)  | 0 / 3 (0.00%)  |
|                                                                                                                                                                                      | 1                                                       | 7               | 0              |
|                                                                                                                                                                                      | Additional description: FALL                            |                 |                |
|                                                                                                                                                                                      | 1 / 3 (33.33%)                                          | 0 / 3 (0.00%)   | 2 / 3 (66.67%) |
| <p>FALL</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                                           | 1                                                       | 0               | 2              |
|                                                                                                                                                                                      | Additional description: FRACTURE                        |                 |                |
|                                                                                                                                                                                      | 0 / 3 (0.00%)                                           | 0 / 3 (0.00%)   | 0 / 3 (0.00%)  |
|                                                                                                                                                                                      | 0                                                       | 0               | 0              |
|                                                                                                                                                                                      | Additional description: INJURY TO SUPERIOR VENA CAVA    |                 |                |
|                                                                                                                                                                                      |                                                         |                 |                |
| <p>FRACTURE</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                                       | Additional description: INJURY TO SUPERIOR VENA CAVA    |                 |                |
|                                                                                                                                                                                      |                                                         |                 |                |
|                                                                                                                                                                                      | Additional description: INJURY TO SUPERIOR VENA CAVA    |                 |                |
|                                                                                                                                                                                      |                                                         |                 |                |
|                                                                                                                                                                                      | Additional description: INJURY TO SUPERIOR VENA CAVA    |                 |                |
|                                                                                                                                                                                      |                                                         |                 |                |

|                                                                 |                                                                                         |                |               |
|-----------------------------------------------------------------|-----------------------------------------------------------------------------------------|----------------|---------------|
| systematic                                                      |                                                                                         |                |               |
| subjects affected / exposed                                     | 1 / 3 (33.33%)                                                                          | 0 / 3 (0.00%)  | 0 / 3 (0.00%) |
| occurrences (all)                                               | 1                                                                                       | 0              | 0             |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS - OTHER, SPECIFY | Additional description: INJURY, POISONING AND PROCEDURAL COMPLICATIONS - OTHER, SPECIFY |                |               |
| alternative assessment type: Non-systematic                     |                                                                                         |                |               |
| subjects affected / exposed                                     | 1 / 3 (33.33%)                                                                          | 0 / 3 (0.00%)  | 0 / 3 (0.00%) |
| occurrences (all)                                               | 2                                                                                       | 0              | 0             |
| Cardiac disorders                                               |                                                                                         |                |               |
| ATRIAL FIBRILLATION                                             | Additional description: ATRIAL FIBRILLATION                                             |                |               |
| alternative assessment type: Non-systematic                     |                                                                                         |                |               |
| subjects affected / exposed                                     | 2 / 3 (66.67%)                                                                          | 0 / 3 (0.00%)  | 0 / 3 (0.00%) |
| occurrences (all)                                               | 2                                                                                       | 0              | 0             |
| CHEST PAIN - CARDIAC                                            | Additional description: CHEST PAIN - CARDIAC                                            |                |               |
| alternative assessment type: Non-systematic                     |                                                                                         |                |               |
| subjects affected / exposed                                     | 0 / 3 (0.00%)                                                                           | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all)                                               | 0                                                                                       | 1              | 0             |
| Nervous system disorders                                        |                                                                                         |                |               |
| DIZZINESS                                                       | Additional description: DIZZINESS                                                       |                |               |
| alternative assessment type: Non-systematic                     |                                                                                         |                |               |
| subjects affected / exposed                                     | 0 / 3 (0.00%)                                                                           | 0 / 3 (0.00%)  | 0 / 3 (0.00%) |
| occurrences (all)                                               | 0                                                                                       | 0              | 0             |
| HEADACHE                                                        | Additional description: HEADACHE                                                        |                |               |
| alternative assessment type: Non-systematic                     |                                                                                         |                |               |
| subjects affected / exposed                                     | 1 / 3 (33.33%)                                                                          | 0 / 3 (0.00%)  | 0 / 3 (0.00%) |
| occurrences (all)                                               | 1                                                                                       | 0              | 0             |
| LETHARGY                                                        | Additional description: LETHARGY                                                        |                |               |
| alternative assessment type: Non-systematic                     |                                                                                         |                |               |
| subjects affected / exposed                                     | 0 / 3 (0.00%)                                                                           | 0 / 3 (0.00%)  | 0 / 3 (0.00%) |
| occurrences (all)                                               | 0                                                                                       | 0              | 0             |
| MEMORY IMPAIRMENT                                               | Additional description: MEMORY IMPAIRMENT                                               |                |               |
| alternative assessment type: Non-systematic                     |                                                                                         |                |               |
| subjects affected / exposed                                     | 0 / 3 (0.00%)                                                                           | 0 / 3 (0.00%)  | 0 / 3 (0.00%) |
| occurrences (all)                                               | 0                                                                                       | 0              | 0             |
| MOVEMENTS INVOLUNTARY                                           | Additional description: MOVEMENTS INVOLUNTARY                                           |                |               |

|                                                                                                 |                                                                      |                    |                     |
|-------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|--------------------|---------------------|
| alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0                                                   | 0 / 3 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0  |
| NERVOUS SYSTEM DISORDERS - OTHER, SPECIFY                                                       | Additional description: NERVOUS SYSTEM DISORDERS - OTHER, SPECIFY    |                    |                     |
| alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 1 / 3 (33.33%)<br>1                                                  | 0 / 3 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0  |
| NEURALGIA                                                                                       | Additional description: NEURALGIA                                    |                    |                     |
| alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0                                                   | 0 / 3 (0.00%)<br>0 | 1 / 3 (33.33%)<br>1 |
| OLFACTORY NERVE DISORDER                                                                        | Additional description: OLFACTORY NERVE DISORDER                     |                    |                     |
| alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0                                                   | 0 / 3 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0  |
| Blood and lymphatic system disorders                                                            |                                                                      |                    |                     |
| ANEMIA                                                                                          | Additional description: ANEMIA                                       |                    |                     |
| alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0                                                   | 0 / 3 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0  |
| THROMBOTIC THROMBOCYTOPENIC PURPURA                                                             | Additional description: THROMBOTIC THROMBOCYTOPENIC PURPURA          |                    |                     |
| alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0                                                   | 0 / 3 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0  |
| Ear and labyrinth disorders                                                                     |                                                                      |                    |                     |
| EAR AND LABYRINTH DISORDERS - OTHER, SPECIFY                                                    | Additional description: EAR AND LABYRINTH DISORDERS - OTHER, SPECIFY |                    |                     |
| alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 1 / 3 (33.33%)<br>1                                                  | 0 / 3 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0  |
| EAR PAIN                                                                                        | Additional description: EAR PAIN                                     |                    |                     |
| alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0                                                   | 0 / 3 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0  |
| Eye disorders                                                                                   |                                                                      |                    |                     |

|                                                                                                                                                |                                                                     |                      |                      |
|------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------|----------------------|----------------------|
| BLURRED VISION<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                              | Additional description: BLURRED VISION                              |                      |                      |
|                                                                                                                                                | 0 / 3 (0.00%)<br>0                                                  | 0 / 3 (0.00%)<br>0   | 0 / 3 (0.00%)<br>0   |
|                                                                                                                                                |                                                                     |                      |                      |
| EYE DISORDERS - OTHER, SPECIFY<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)              | Additional description: EYE DISORDERS - OTHER, SPECIFY              |                      |                      |
|                                                                                                                                                | 1 / 3 (33.33%)<br>1                                                 | 0 / 3 (0.00%)<br>0   | 0 / 3 (0.00%)<br>0   |
|                                                                                                                                                |                                                                     |                      |                      |
| Gastrointestinal disorders                                                                                                                     |                                                                     |                      |                      |
|                                                                                                                                                | Additional description: ABDOMINAL PAIN                              |                      |                      |
| ABDOMINAL PAIN<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 3 (0.00%)<br>0                                                  | 1 / 3 (33.33%)<br>1  | 0 / 3 (0.00%)<br>0   |
|                                                                                                                                                |                                                                     |                      |                      |
|                                                                                                                                                |                                                                     |                      |                      |
| BLOATING<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                    | Additional description: BLOATING                                    |                      |                      |
|                                                                                                                                                | 0 / 3 (0.00%)<br>0                                                  | 0 / 3 (0.00%)<br>0   | 0 / 3 (0.00%)<br>0   |
|                                                                                                                                                |                                                                     |                      |                      |
| CONSTIPATION<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                | Additional description: CONSTIPATION                                |                      |                      |
|                                                                                                                                                | 3 / 3 (100.00%)<br>5                                                | 1 / 3 (33.33%)<br>3  | 1 / 3 (33.33%)<br>1  |
|                                                                                                                                                |                                                                     |                      |                      |
| DIARRHEA<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                    | Additional description: DIARRHEA                                    |                      |                      |
|                                                                                                                                                | 3 / 3 (100.00%)<br>8                                                | 3 / 3 (100.00%)<br>6 | 2 / 3 (66.67%)<br>20 |
|                                                                                                                                                |                                                                     |                      |                      |
| DYSPEPSIA<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                   | Additional description: DYSPEPSIA                                   |                      |                      |
|                                                                                                                                                | 0 / 3 (0.00%)<br>0                                                  | 0 / 3 (0.00%)<br>0   | 0 / 3 (0.00%)<br>0   |
|                                                                                                                                                |                                                                     |                      |                      |
| GASTROINTESTINAL DISORDERS - OTHER, SPECIFY<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | Additional description: GASTROINTESTINAL DISORDERS - OTHER, SPECIFY |                      |                      |
|                                                                                                                                                | 0 / 3 (0.00%)<br>0                                                  | 0 / 3 (0.00%)<br>0   | 1 / 3 (33.33%)<br>1  |
|                                                                                                                                                |                                                                     |                      |                      |
| GASTROINTESTINAL PAIN<br>alternative assessment type: Non-                                                                                     | Additional description: GASTROINTESTINAL PAIN                       |                      |                      |
|                                                                                                                                                |                                                                     |                      |                      |



|                                             |                                                    |                 |                |
|---------------------------------------------|----------------------------------------------------|-----------------|----------------|
| systematic                                  |                                                    |                 |                |
| subjects affected / exposed                 | 0 / 3 (0.00%)                                      | 0 / 3 (0.00%)   | 1 / 3 (33.33%) |
| occurrences (all)                           | 0                                                  | 0               | 1              |
| MUCOSITIS ORAL                              | Additional description: MUCOSITIS ORAL             |                 |                |
| alternative assessment type: Non-systematic |                                                    |                 |                |
| subjects affected / exposed                 | 1 / 3 (33.33%)                                     | 0 / 3 (0.00%)   | 0 / 3 (0.00%)  |
| occurrences (all)                           | 1                                                  | 0               | 0              |
| NAUSEA                                      | Additional description: NAUSEA                     |                 |                |
| alternative assessment type: Non-systematic |                                                    |                 |                |
| subjects affected / exposed                 | 3 / 3 (100.00%)                                    | 3 / 3 (100.00%) | 2 / 3 (66.67%) |
| occurrences (all)                           | 8                                                  | 7               | 36             |
| ORAL PAIN                                   | Additional description: ORAL PAIN                  |                 |                |
| alternative assessment type: Non-systematic |                                                    |                 |                |
| subjects affected / exposed                 | 1 / 3 (33.33%)                                     | 0 / 3 (0.00%)   | 0 / 3 (0.00%)  |
| occurrences (all)                           | 3                                                  | 0               | 0              |
| SALIVARY DUCT INFLAMMATION                  | Additional description: SALIVARY DUCT INFLAMMATION |                 |                |
| alternative assessment type: Non-systematic |                                                    |                 |                |
| subjects affected / exposed                 | 0 / 3 (0.00%)                                      | 0 / 3 (0.00%)   | 0 / 3 (0.00%)  |
| occurrences (all)                           | 0                                                  | 0               | 0              |
| STOMACH PAIN                                | Additional description: STOMACH PAIN               |                 |                |
| alternative assessment type: Non-systematic |                                                    |                 |                |
| subjects affected / exposed                 | 0 / 3 (0.00%)                                      | 0 / 3 (0.00%)   | 0 / 3 (0.00%)  |
| occurrences (all)                           | 0                                                  | 0               | 0              |
| VOMITING                                    | Additional description: VOMITING                   |                 |                |
| alternative assessment type: Non-systematic |                                                    |                 |                |
| subjects affected / exposed                 | 2 / 3 (66.67%)                                     | 1 / 3 (33.33%)  | 1 / 3 (33.33%) |
| occurrences (all)                           | 2                                                  | 2               | 13             |
| Skin and subcutaneous tissue disorders      |                                                    |                 |                |
| DRY SKIN                                    | Additional description: DRY SKIN                   |                 |                |
| alternative assessment type: Non-systematic |                                                    |                 |                |
| subjects affected / exposed                 | 0 / 3 (0.00%)                                      | 0 / 3 (0.00%)   | 0 / 3 (0.00%)  |
| occurrences (all)                           | 0                                                  | 0               | 0              |
| RASH MACULO-PAPULAR                         | Additional description: RASH MACULO-PAPULAR        |                 |                |
| alternative assessment type: Non-systematic |                                                    |                 |                |

|                                                         |                                                                                 |                |                |
|---------------------------------------------------------|---------------------------------------------------------------------------------|----------------|----------------|
| subjects affected / exposed                             | 0 / 3 (0.00%)                                                                   | 0 / 3 (0.00%)  | 1 / 3 (33.33%) |
| occurrences (all)                                       | 0                                                                               | 0              | 2              |
| SCALP PAIN                                              | Additional description: SCALP PAIN                                              |                |                |
| alternative assessment type: Non-systematic             |                                                                                 |                |                |
| subjects affected / exposed                             | 0 / 3 (0.00%)                                                                   | 0 / 3 (0.00%)  | 1 / 3 (33.33%) |
| occurrences (all)                                       | 0                                                                               | 0              | 1              |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS - OTHER, SPECIFY | Additional description: SKIN AND SUBCUTANEOUS TISSUE DISORDERS - OTHER, SPECIFY |                |                |
| alternative assessment type: Non-systematic             |                                                                                 |                |                |
| subjects affected / exposed                             | 2 / 3 (66.67%)                                                                  | 2 / 3 (66.67%) | 0 / 3 (0.00%)  |
| occurrences (all)                                       | 5                                                                               | 2              | 0              |
| Renal and urinary disorders                             |                                                                                 |                |                |
| CYSTITIS NONINFECTIVE                                   | Additional description: CYSTITIS NONINFECTIVE                                   |                |                |
| alternative assessment type: Non-systematic             |                                                                                 |                |                |
| subjects affected / exposed                             | 0 / 3 (0.00%)                                                                   | 0 / 3 (0.00%)  | 1 / 3 (33.33%) |
| occurrences (all)                                       | 0                                                                               | 0              | 5              |
| HEMATURIA                                               | Additional description: HEMATURIA                                               |                |                |
| alternative assessment type: Non-systematic             |                                                                                 |                |                |
| subjects affected / exposed                             | 0 / 3 (0.00%)                                                                   | 1 / 3 (33.33%) | 0 / 3 (0.00%)  |
| occurrences (all)                                       | 0                                                                               | 1              | 0              |
| RENAL AND URINARY DISORDERS - OTHER, SPECIFY            | Additional description: RENAL AND URINARY DISORDERS - OTHER, SPECIFY            |                |                |
| alternative assessment type: Non-systematic             |                                                                                 |                |                |
| subjects affected / exposed                             | 0 / 3 (0.00%)                                                                   | 1 / 3 (33.33%) | 1 / 3 (33.33%) |
| occurrences (all)                                       | 0                                                                               | 3              | 1              |
| URINARY FREQUENCY                                       | Additional description: URINARY FREQUENCY                                       |                |                |
| alternative assessment type: Non-systematic             |                                                                                 |                |                |
| subjects affected / exposed                             | 1 / 3 (33.33%)                                                                  | 1 / 3 (33.33%) | 0 / 3 (0.00%)  |
| occurrences (all)                                       | 1                                                                               | 1              | 0              |
| URINARY RETENTION                                       | Additional description: URINARY RETENTION                                       |                |                |
| alternative assessment type: Non-systematic             |                                                                                 |                |                |
| subjects affected / exposed                             | 0 / 3 (0.00%)                                                                   | 0 / 3 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)                                       | 0                                                                               | 0              | 0              |
| Musculoskeletal and connective tissue disorders         |                                                                                 |                |                |

|                                                                                                                                                                    |                                                                                         |                     |                     |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|---------------------|---------------------|
| BACK PAIN<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                                       | Additional description: BACK PAIN                                                       |                     |                     |
|                                                                                                                                                                    | 0 / 3 (0.00%)<br>0                                                                      | 1 / 3 (33.33%)<br>2 | 1 / 3 (33.33%)<br>1 |
|                                                                                                                                                                    |                                                                                         |                     |                     |
| BONE PAIN<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                                       | Additional description: BONE PAIN                                                       |                     |                     |
|                                                                                                                                                                    | 0 / 3 (0.00%)<br>0                                                                      | 0 / 3 (0.00%)<br>0  | 1 / 3 (33.33%)<br>3 |
|                                                                                                                                                                    |                                                                                         |                     |                     |
| BUTTOCK PAIN<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                                    | Additional description: BUTTOCK PAIN                                                    |                     |                     |
|                                                                                                                                                                    | 1 / 3 (33.33%)<br>1                                                                     | 0 / 3 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  |
|                                                                                                                                                                    |                                                                                         |                     |                     |
| CHEST WALL PAIN<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                                 | Additional description: CHEST WALL PAIN                                                 |                     |                     |
|                                                                                                                                                                    | 1 / 3 (33.33%)<br>1                                                                     | 0 / 3 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  |
|                                                                                                                                                                    |                                                                                         |                     |                     |
| FLANK PAIN<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                                      | Additional description: FLANK PAIN                                                      |                     |                     |
|                                                                                                                                                                    | 0 / 3 (0.00%)<br>0                                                                      | 0 / 3 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  |
|                                                                                                                                                                    |                                                                                         |                     |                     |
| MUSCLE WEAKNESS LOWER LIMB<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                      | Additional description: MUSCLE WEAKNESS LOWER LIMB                                      |                     |                     |
|                                                                                                                                                                    | 0 / 3 (0.00%)<br>0                                                                      | 0 / 3 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  |
|                                                                                                                                                                    |                                                                                         |                     |                     |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDER - OTHER, SPECIFY<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | Additional description: MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDER - OTHER, SPECIFY |                     |                     |
|                                                                                                                                                                    | 1 / 3 (33.33%)<br>2                                                                     | 0 / 3 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  |
|                                                                                                                                                                    |                                                                                         |                     |                     |
| NECK PAIN<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                                       | Additional description: NECK PAIN                                                       |                     |                     |
|                                                                                                                                                                    | 0 / 3 (0.00%)<br>0                                                                      | 0 / 3 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  |
|                                                                                                                                                                    |                                                                                         |                     |                     |
| Infections and infestations                                                                                                                                        |                                                                                         |                     |                     |

|                                                                                                                                                 |                                                                      |               |                |
|-------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|---------------|----------------|
| BLADDER INFECTION<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                            | Additional description: BLADDER INFECTION                            |               |                |
|                                                                                                                                                 | 0 / 3 (0.00%)                                                        | 0 / 3 (0.00%) | 0 / 3 (0.00%)  |
|                                                                                                                                                 | 0                                                                    | 0             | 0              |
| INFECTIONS AND INFESTATIONS - OTHER, SPECIFY<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | Additional description: INFECTIONS AND INFESTATIONS - OTHER, SPECIFY |               |                |
|                                                                                                                                                 | 1 / 3 (33.33%)                                                       | 0 / 3 (0.00%) | 2 / 3 (66.67%) |
|                                                                                                                                                 | 2                                                                    | 0             | 2              |
| LARYNGITIS<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                   | Additional description: LARYNGITIS                                   |               |                |
|                                                                                                                                                 | 0 / 3 (0.00%)                                                        | 0 / 3 (0.00%) | 0 / 3 (0.00%)  |
|                                                                                                                                                 | 0                                                                    | 0             | 0              |
| LUNG INFECTION<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                               | Additional description: LUNG INFECTION                               |               |                |
|                                                                                                                                                 | 1 / 3 (33.33%)                                                       | 0 / 3 (0.00%) | 0 / 3 (0.00%)  |
|                                                                                                                                                 | 1                                                                    | 0             | 0              |
| PENILE INFECTION<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                             | Additional description: PENILE INFECTION                             |               |                |
|                                                                                                                                                 | 0 / 3 (0.00%)                                                        | 0 / 3 (0.00%) | 0 / 3 (0.00%)  |
|                                                                                                                                                 | 0                                                                    | 0             | 0              |
| PHARYNGITIS<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                  | Additional description: PHARYNGITIS                                  |               |                |
|                                                                                                                                                 | 0 / 3 (0.00%)                                                        | 0 / 3 (0.00%) | 0 / 3 (0.00%)  |
|                                                                                                                                                 | 0                                                                    | 0             | 0              |
| RHINITIS INFECTIVE<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                           | Additional description: RHINITIS INFECTIVE                           |               |                |
|                                                                                                                                                 | 0 / 3 (0.00%)                                                        | 0 / 3 (0.00%) | 0 / 3 (0.00%)  |
|                                                                                                                                                 | 0                                                                    | 0             | 0              |
| SINUSITIS<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                    | Additional description: SINUSITIS                                    |               |                |
|                                                                                                                                                 | 0 / 3 (0.00%)                                                        | 0 / 3 (0.00%) | 0 / 3 (0.00%)  |
|                                                                                                                                                 | 0                                                                    | 0             | 0              |
| SKIN INFECTION<br>alternative assessment type: Non-systematic                                                                                   | Additional description: SKIN INFECTION                               |               |                |
|                                                                                                                                                 |                                                                      |               |                |
|                                                                                                                                                 |                                                                      |               |                |

|                                             |                                                     |               |                |
|---------------------------------------------|-----------------------------------------------------|---------------|----------------|
| subjects affected / exposed                 | 0 / 3 (0.00%)                                       | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all)                           | 0                                                   | 0             | 1              |
| <b>SOFT TISSUE INFECTION</b>                | Additional description: SOFT TISSUE INFECTION       |               |                |
| alternative assessment type: Non-systematic |                                                     |               |                |
| subjects affected / exposed                 | 0 / 3 (0.00%)                                       | 0 / 3 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                           | 0                                                   | 0             | 0              |
| <b>UPPER RESPIRATORY INFECTION</b>          | Additional description: UPPER RESPIRATORY INFECTION |               |                |
| alternative assessment type: Non-systematic |                                                     |               |                |
| subjects affected / exposed                 | 1 / 3 (33.33%)                                      | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all)                           | 1                                                   | 0             | 1              |
| <b>URINARY TRACT INFECTION</b>              | Additional description: URINARY TRACT INFECTION     |               |                |
| alternative assessment type: Non-systematic |                                                     |               |                |
| subjects affected / exposed                 | 0 / 3 (0.00%)                                       | 0 / 3 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                           | 0                                                   | 0             | 0              |
| <b>UTERINE INFECTION</b>                    | Additional description: UTERINE INFECTION           |               |                |
| alternative assessment type: Non-systematic |                                                     |               |                |
| subjects affected / exposed                 | 0 / 3 (0.00%)                                       | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all)                           | 0                                                   | 0             | 1              |
| <b>Metabolism and nutrition disorders</b>   |                                                     |               |                |
| <b>ANOREXIA</b>                             | Additional description: ANOREXIA                    |               |                |
| alternative assessment type: Non-systematic |                                                     |               |                |
| subjects affected / exposed                 | 1 / 3 (33.33%)                                      | 0 / 3 (0.00%) | 2 / 3 (66.67%) |
| occurrences (all)                           | 2                                                   | 0             | 28             |
| <b>DEHYDRATION</b>                          | Additional description: DEHYDRATION                 |               |                |
| alternative assessment type: Non-systematic |                                                     |               |                |
| subjects affected / exposed                 | 0 / 3 (0.00%)                                       | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all)                           | 0                                                   | 0             | 1              |
| <b>HYPERGLYCEMIA</b>                        | Additional description: HYPERGLYCEMIA               |               |                |
| alternative assessment type: Non-systematic |                                                     |               |                |
| subjects affected / exposed                 | 0 / 3 (0.00%)                                       | 0 / 3 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                           | 0                                                   | 0             | 0              |
| <b>HYPOCALCEMIA</b>                         | Additional description: HYPOCALCEMIA                |               |                |
| alternative assessment type: Non-systematic |                                                     |               |                |

|                                             |                                      |               |                |
|---------------------------------------------|--------------------------------------|---------------|----------------|
| subjects affected / exposed                 | 1 / 3 (33.33%)                       | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all)                           | 1                                    | 0             | 1              |
| HYPOGLYCEMIA                                | Additional description: HYPOGLYCEMIA |               |                |
| alternative assessment type: Non-systematic |                                      |               |                |
| subjects affected / exposed                 | 0 / 3 (0.00%)                        | 0 / 3 (0.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                           | 0                                    | 0             | 0              |

| Non-serious adverse events                                                           | Cohort 1E                                                                                                    | Cohort 2        | Cohort 3B       |
|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|-----------------|-----------------|
| Total subjects affected by non-serious adverse events                                |                                                                                                              |                 |                 |
| subjects affected / exposed                                                          | 3 / 3 (100.00%)                                                                                              | 3 / 3 (100.00%) | 7 / 7 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps)                  |                                                                                                              |                 |                 |
| NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - OTHER, SPECIFY | Additional description: NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - OTHER, SPECIFY |                 |                 |
| alternative assessment type: Non-systematic                                          |                                                                                                              |                 |                 |
| subjects affected / exposed                                                          | 1 / 3 (33.33%)                                                                                               | 0 / 3 (0.00%)   | 1 / 7 (14.29%)  |
| occurrences (all)                                                                    | 1                                                                                                            | 0               | 1               |
| Vascular disorders                                                                   |                                                                                                              |                 |                 |
| FLUSHING                                                                             | Additional description: FLUSHING                                                                             |                 |                 |
| alternative assessment type: Non-systematic                                          |                                                                                                              |                 |                 |
| subjects affected / exposed                                                          | 0 / 3 (0.00%)                                                                                                | 0 / 3 (0.00%)   | 1 / 7 (14.29%)  |
| occurrences (all)                                                                    | 0                                                                                                            | 0               | 1               |
| HOT FLASHES                                                                          | Additional description: HOT FLASHES                                                                          |                 |                 |
| alternative assessment type: Non-systematic                                          |                                                                                                              |                 |                 |
| subjects affected / exposed                                                          | 0 / 3 (0.00%)                                                                                                | 0 / 3 (0.00%)   | 0 / 7 (0.00%)   |
| occurrences (all)                                                                    | 0                                                                                                            | 0               | 0               |
| HYPERTENSION                                                                         | Additional description: HYPERTENSION                                                                         |                 |                 |
| alternative assessment type: Non-systematic                                          |                                                                                                              |                 |                 |
| subjects affected / exposed                                                          | 0 / 3 (0.00%)                                                                                                | 0 / 3 (0.00%)   | 2 / 7 (28.57%)  |
| occurrences (all)                                                                    | 0                                                                                                            | 0               | 2               |
| HYPOTENSION                                                                          | Additional description: HYPOTENSION                                                                          |                 |                 |
| alternative assessment type: Non-systematic                                          |                                                                                                              |                 |                 |
| subjects affected / exposed                                                          | 0 / 3 (0.00%)                                                                                                | 0 / 3 (0.00%)   | 1 / 7 (14.29%)  |
| occurrences (all)                                                                    | 0                                                                                                            | 0               | 2               |
| PHLEBITIS                                                                            | Additional description: PHLEBITIS                                                                            |                 |                 |
| alternative assessment type: Non-systematic                                          |                                                                                                              |                 |                 |

|                                                                       |                                                                                               |                |                |
|-----------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|----------------|----------------|
| subjects affected / exposed                                           | 0 / 3 (0.00%)                                                                                 | 0 / 3 (0.00%)  | 0 / 7 (0.00%)  |
| occurrences (all)                                                     | 0                                                                                             | 0              | 0              |
| THROMBOEMBOLIC EVENT                                                  | Additional description: THROMBOEMBOLIC EVENT                                                  |                |                |
| alternative assessment type: Non-systematic                           |                                                                                               |                |                |
| subjects affected / exposed                                           | 0 / 3 (0.00%)                                                                                 | 0 / 3 (0.00%)  | 1 / 7 (14.29%) |
| occurrences (all)                                                     | 0                                                                                             | 0              | 1              |
| General disorders and administration site conditions                  |                                                                                               |                |                |
| EDEMA FACE                                                            | Additional description: EDEMA FACE                                                            |                |                |
| alternative assessment type: Non-systematic                           |                                                                                               |                |                |
| subjects affected / exposed                                           | 0 / 3 (0.00%)                                                                                 | 0 / 3 (0.00%)  | 0 / 7 (0.00%)  |
| occurrences (all)                                                     | 0                                                                                             | 0              | 0              |
| EDEMA LIMBS                                                           | Additional description: EDEMA LIMBS                                                           |                |                |
| alternative assessment type: Non-systematic                           |                                                                                               |                |                |
| subjects affected / exposed                                           | 0 / 3 (0.00%)                                                                                 | 1 / 3 (33.33%) | 0 / 7 (0.00%)  |
| occurrences (all)                                                     | 0                                                                                             | 1              | 0              |
| FATIGUE                                                               | Additional description: FATIGUE                                                               |                |                |
| alternative assessment type: Non-systematic                           |                                                                                               |                |                |
| subjects affected / exposed                                           | 3 / 3 (100.00%)                                                                               | 1 / 3 (33.33%) | 5 / 7 (71.43%) |
| occurrences (all)                                                     | 18                                                                                            | 1              | 21             |
| FEVER                                                                 | Additional description: FEVER                                                                 |                |                |
| alternative assessment type: Non-systematic                           |                                                                                               |                |                |
| subjects affected / exposed                                           | 0 / 3 (0.00%)                                                                                 | 0 / 3 (0.00%)  | 0 / 7 (0.00%)  |
| occurrences (all)                                                     | 0                                                                                             | 0              | 0              |
| FLU LIKE SYMPTOMS                                                     | Additional description: FLU LIKE SYMPTOMS                                                     |                |                |
| alternative assessment type: Non-systematic                           |                                                                                               |                |                |
| subjects affected / exposed                                           | 2 / 3 (66.67%)                                                                                | 1 / 3 (33.33%) | 1 / 7 (14.29%) |
| occurrences (all)                                                     | 2                                                                                             | 2              | 1              |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - OTHER, SPECIFY | Additional description: GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - OTHER, SPECIFY |                |                |
| alternative assessment type: Non-systematic                           |                                                                                               |                |                |
| subjects affected / exposed                                           | 1 / 3 (33.33%)                                                                                | 0 / 3 (0.00%)  | 2 / 7 (28.57%) |
| occurrences (all)                                                     | 2                                                                                             | 0              | 4              |
| HYPOTHERMIA                                                           | Additional description: HYPOTHERMIA                                                           |                |                |
| alternative assessment type: Non-systematic                           |                                                                                               |                |                |

|                                                           |                                                                                   |                |                |
|-----------------------------------------------------------|-----------------------------------------------------------------------------------|----------------|----------------|
| subjects affected / exposed                               | 0 / 3 (0.00%)                                                                     | 0 / 3 (0.00%)  | 1 / 7 (14.29%) |
| occurrences (all)                                         | 0                                                                                 | 0              | 1              |
| MALAISE                                                   | Additional description: MALAISE                                                   |                |                |
| alternative assessment type: Non-systematic               |                                                                                   |                |                |
| subjects affected / exposed                               | 1 / 3 (33.33%)                                                                    | 0 / 3 (0.00%)  | 3 / 7 (42.86%) |
| occurrences (all)                                         | 9                                                                                 | 0              | 6              |
| NON-CARDIAC CHEST PAIN                                    | Additional description: NON-CARDIAC CHEST PAIN                                    |                |                |
| alternative assessment type: Non-systematic               |                                                                                   |                |                |
| subjects affected / exposed                               | 1 / 3 (33.33%)                                                                    | 0 / 3 (0.00%)  | 0 / 7 (0.00%)  |
| occurrences (all)                                         | 1                                                                                 | 0              | 0              |
| PAIN                                                      | Additional description: PAIN                                                      |                |                |
| alternative assessment type: Non-systematic               |                                                                                   |                |                |
| subjects affected / exposed                               | 3 / 3 (100.00%)                                                                   | 1 / 3 (33.33%) | 4 / 7 (57.14%) |
| occurrences (all)                                         | 6                                                                                 | 3              | 7              |
| Immune system disorders                                   |                                                                                   |                |                |
| ALLERGIC REACTION                                         | Additional description: ALLERGIC REACTION                                         |                |                |
| alternative assessment type: Non-systematic               |                                                                                   |                |                |
| subjects affected / exposed                               | 0 / 3 (0.00%)                                                                     | 0 / 3 (0.00%)  | 1 / 7 (14.29%) |
| occurrences (all)                                         | 0                                                                                 | 0              | 1              |
| Reproductive system and breast disorders                  |                                                                                   |                |                |
| GYNECOMASTIA                                              | Additional description: GYNECOMASTIA                                              |                |                |
| alternative assessment type: Non-systematic               |                                                                                   |                |                |
| subjects affected / exposed                               | 1 / 3 (33.33%)                                                                    | 0 / 3 (0.00%)  | 0 / 7 (0.00%)  |
| occurrences (all)                                         | 1                                                                                 | 0              | 0              |
| PELVIC PAIN                                               | Additional description: PELVIC PAIN                                               |                |                |
| alternative assessment type: Non-systematic               |                                                                                   |                |                |
| subjects affected / exposed                               | 0 / 3 (0.00%)                                                                     | 0 / 3 (0.00%)  | 2 / 7 (28.57%) |
| occurrences (all)                                         | 0                                                                                 | 0              | 2              |
| REPRODUCTIVE SYSTEM AND BREAST DISORDERS - OTHER, SPECIFY | Additional description: REPRODUCTIVE SYSTEM AND BREAST DISORDERS - OTHER, SPECIFY |                |                |
| alternative assessment type: Non-systematic               |                                                                                   |                |                |
| subjects affected / exposed                               | 0 / 3 (0.00%)                                                                     | 0 / 3 (0.00%)  | 1 / 7 (14.29%) |
| occurrences (all)                                         | 0                                                                                 | 0              | 2              |
| Respiratory, thoracic and mediastinal disorders           |                                                                                   |                |                |



|                                                                                                                                                                     |                                                                                          |                     |                     |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|---------------------|---------------------|
| COUGH<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                                            | Additional description: COUGH                                                            |                     |                     |
|                                                                                                                                                                     | 1 / 3 (33.33%)<br>3                                                                      | 0 / 3 (0.00%)<br>0  | 1 / 7 (14.29%)<br>3 |
| DYSPNEA<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                                          | Additional description: DYSPNEA                                                          |                     |                     |
|                                                                                                                                                                     | 1 / 3 (33.33%)<br>1                                                                      | 0 / 3 (0.00%)<br>0  | 4 / 7 (57.14%)<br>6 |
| EPISTAXIS<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                                        | Additional description: EPISTAXIS                                                        |                     |                     |
|                                                                                                                                                                     | 0 / 3 (0.00%)<br>0                                                                       | 1 / 3 (33.33%)<br>2 | 1 / 7 (14.29%)<br>1 |
| LARYNGEAL INFLAMMATION<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                           | Additional description: LARYNGEAL INFLAMMATION                                           |                     |                     |
|                                                                                                                                                                     | 1 / 3 (33.33%)<br>2                                                                      | 0 / 3 (0.00%)<br>0  | 0 / 7 (0.00%)<br>0  |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - OTHER, SPECIFY<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | Additional description: RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - OTHER, SPECIFY |                     |                     |
|                                                                                                                                                                     | 1 / 3 (33.33%)<br>2                                                                      | 0 / 3 (0.00%)<br>0  | 2 / 7 (28.57%)<br>2 |
| SLEEP APNEA<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                                      | Additional description: SLEEP APNEA                                                      |                     |                     |
|                                                                                                                                                                     | 1 / 3 (33.33%)<br>1                                                                      | 0 / 3 (0.00%)<br>0  | 0 / 7 (0.00%)<br>0  |
| WHEEZING<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                                         | Additional description: WHEEZING                                                         |                     |                     |
|                                                                                                                                                                     | 0 / 3 (0.00%)<br>0                                                                       | 0 / 3 (0.00%)<br>0  | 0 / 7 (0.00%)<br>0  |
| Psychiatric disorders<br>ANXIETY<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                 | Additional description: ANXIETY                                                          |                     |                     |
|                                                                                                                                                                     | 0 / 3 (0.00%)<br>0                                                                       | 0 / 3 (0.00%)<br>0  | 0 / 7 (0.00%)<br>0  |
| CONFUSION                                                                                                                                                           | Additional description: CONFUSION                                                        |                     |                     |

|                                                                                                 |                                                                         |                     |                     |
|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|---------------------|---------------------|
| alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0                                                      | 0 / 3 (0.00%)<br>0  | 1 / 7 (14.29%)<br>1 |
| DEPRESSION                                                                                      | Additional description: DEPRESSION                                      |                     |                     |
| alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0                                                      | 1 / 3 (33.33%)<br>1 | 0 / 7 (0.00%)<br>0  |
| PSYCHIATRIC DISORDERS - OTHER, SPECIFY                                                          | Additional description: PSYCHIATRIC DISORDERS - OTHER, SPECIFY          |                     |                     |
| alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0                                                      | 0 / 3 (0.00%)<br>0  | 2 / 7 (28.57%)<br>2 |
| Investigations                                                                                  |                                                                         |                     |                     |
| ACTIVATED PARTIAL THROMBOPLASTIN TIME PROLONGED                                                 | Additional description: ACTIVATED PARTIAL THROMBOPLASTIN TIME PROLONGED |                     |                     |
| alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 1 / 3 (33.33%)<br>1                                                     | 0 / 3 (0.00%)<br>0  | 0 / 7 (0.00%)<br>0  |
| INVESTIGATIONS - OTHER, SPECIFY                                                                 | Additional description: INVESTIGATIONS - OTHER, SPECIFY                 |                     |                     |
| alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0                                                      | 0 / 3 (0.00%)<br>0  | 0 / 7 (0.00%)<br>0  |
| NEUTROPHIL COUNT DECREASED                                                                      | Additional description: NEUTROPHIL COUNT DECREASED                      |                     |                     |
| alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 1 / 3 (33.33%)<br>1                                                     | 1 / 3 (33.33%)<br>1 | 4 / 7 (57.14%)<br>6 |
| PLATELET COUNT DECREASED                                                                        | Additional description: PLATELET COUNT DECREASED                        |                     |                     |
| alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0                                                      | 1 / 3 (33.33%)<br>2 | 4 / 7 (57.14%)<br>6 |
| WEIGHT GAIN                                                                                     | Additional description: WEIGHT GAIN                                     |                     |                     |
| alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 1 / 3 (33.33%)<br>1                                                     | 0 / 3 (0.00%)<br>0  | 0 / 7 (0.00%)<br>0  |
| WEIGHT LOSS                                                                                     | Additional description: WEIGHT LOSS                                     |                     |                     |

|                                                                                                 |                                                                                         |                     |                     |
|-------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|---------------------|---------------------|
| alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0                                                                      | 1 / 3 (33.33%)<br>1 | 0 / 7 (0.00%)<br>0  |
| Injury, poisoning and procedural complications                                                  |                                                                                         |                     |                     |
| BRUISING                                                                                        | Additional description: BRUISING                                                        |                     |                     |
| alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0                                                                      | 0 / 3 (0.00%)<br>0  | 2 / 7 (28.57%)<br>2 |
| FALL                                                                                            | Additional description: FALL                                                            |                     |                     |
| alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0                                                                      | 0 / 3 (0.00%)<br>0  | 1 / 7 (14.29%)<br>1 |
| FRACTURE                                                                                        | Additional description: FRACTURE                                                        |                     |                     |
| alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0                                                                      | 1 / 3 (33.33%)<br>1 | 1 / 7 (14.29%)<br>1 |
| INJURY TO SUPERIOR VENA CAVA                                                                    | Additional description: INJURY TO SUPERIOR VENA CAVA                                    |                     |                     |
| alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0                                                                      | 0 / 3 (0.00%)<br>0  | 0 / 7 (0.00%)<br>0  |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS - OTHER, SPECIFY                                 | Additional description: INJURY, POISONING AND PROCEDURAL COMPLICATIONS - OTHER, SPECIFY |                     |                     |
| alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 1 / 3 (33.33%)<br>1                                                                     | 1 / 3 (33.33%)<br>1 | 2 / 7 (28.57%)<br>2 |
| Cardiac disorders                                                                               |                                                                                         |                     |                     |
| ATRIAL FIBRILLATION                                                                             | Additional description: ATRIAL FIBRILLATION                                             |                     |                     |
| alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0                                                                      | 0 / 3 (0.00%)<br>0  | 0 / 7 (0.00%)<br>0  |
| CHEST PAIN - CARDIAC                                                                            | Additional description: CHEST PAIN - CARDIAC                                            |                     |                     |
| alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0                                                                      | 0 / 3 (0.00%)<br>0  | 0 / 7 (0.00%)<br>0  |
| Nervous system disorders                                                                        |                                                                                         |                     |                     |

|                                                                                                                                              |                                                                   |                     |                     |
|----------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|---------------------|---------------------|
| DIZZINESS<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                 | Additional description: DIZZINESS                                 |                     |                     |
|                                                                                                                                              | 0 / 3 (0.00%)<br>0                                                | 1 / 3 (33.33%)<br>1 | 3 / 7 (42.86%)<br>5 |
|                                                                                                                                              |                                                                   |                     |                     |
| HEADACHE<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                  | Additional description: HEADACHE                                  |                     |                     |
|                                                                                                                                              | 1 / 3 (33.33%)<br>2                                               | 1 / 3 (33.33%)<br>4 | 3 / 7 (42.86%)<br>3 |
|                                                                                                                                              |                                                                   |                     |                     |
| LETHARGY<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                  | Additional description: LETHARGY                                  |                     |                     |
|                                                                                                                                              | 0 / 3 (0.00%)<br>0                                                | 0 / 3 (0.00%)<br>0  | 3 / 7 (42.86%)<br>3 |
|                                                                                                                                              |                                                                   |                     |                     |
| MEMORY IMPAIRMENT<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                         | Additional description: MEMORY IMPAIRMENT                         |                     |                     |
|                                                                                                                                              | 1 / 3 (33.33%)<br>1                                               | 0 / 3 (0.00%)<br>0  | 1 / 7 (14.29%)<br>1 |
|                                                                                                                                              |                                                                   |                     |                     |
| MOVEMENTS INVOLUNTARY<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                     | Additional description: MOVEMENTS INVOLUNTARY                     |                     |                     |
|                                                                                                                                              | 1 / 3 (33.33%)<br>2                                               | 0 / 3 (0.00%)<br>0  | 0 / 7 (0.00%)<br>0  |
|                                                                                                                                              |                                                                   |                     |                     |
| NERVOUS SYSTEM DISORDERS - OTHER, SPECIFY<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | Additional description: NERVOUS SYSTEM DISORDERS - OTHER, SPECIFY |                     |                     |
|                                                                                                                                              | 1 / 3 (33.33%)<br>2                                               | 2 / 3 (66.67%)<br>2 | 2 / 7 (28.57%)<br>4 |
|                                                                                                                                              |                                                                   |                     |                     |
| NEURALGIA<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                 | Additional description: NEURALGIA                                 |                     |                     |
|                                                                                                                                              | 0 / 3 (0.00%)<br>0                                                | 0 / 3 (0.00%)<br>0  | 0 / 7 (0.00%)<br>0  |
|                                                                                                                                              |                                                                   |                     |                     |
| OLFACTORY NERVE DISORDER<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                  | Additional description: OLFACTORY NERVE DISORDER                  |                     |                     |
|                                                                                                                                              | 0 / 3 (0.00%)<br>0                                                | 0 / 3 (0.00%)<br>0  | 1 / 7 (14.29%)<br>1 |
|                                                                                                                                              |                                                                   |                     |                     |
| Blood and lymphatic system disorders                                                                                                         |                                                                   |                     |                     |

|                                                                                                                                                                                |                                                                      |                     |                     |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|---------------------|---------------------|
| ANEMIA<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                                                      | Additional description: ANEMIA                                       |                     |                     |
|                                                                                                                                                                                | 1 / 3 (33.33%)<br>1                                                  | 0 / 3 (0.00%)<br>0  | 3 / 7 (42.86%)<br>4 |
| THROMBOTIC THROMBOCYTOPENIC PURPURA<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                         | Additional description: THROMBOTIC THROMBOCYTOPENIC PURPURA          |                     |                     |
|                                                                                                                                                                                | 1 / 3 (33.33%)<br>1                                                  | 1 / 3 (33.33%)<br>2 | 3 / 7 (42.86%)<br>4 |
| Ear and labyrinth disorders<br>EAR AND LABYRINTH DISORDERS - OTHER, SPECIFY<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | Additional description: EAR AND LABYRINTH DISORDERS - OTHER, SPECIFY |                     |                     |
|                                                                                                                                                                                | 1 / 3 (33.33%)<br>1                                                  | 0 / 3 (0.00%)<br>0  | 0 / 7 (0.00%)<br>0  |
| EAR PAIN<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                                                    | Additional description: EAR PAIN                                     |                     |                     |
|                                                                                                                                                                                | 0 / 3 (0.00%)<br>0                                                   | 1 / 3 (33.33%)<br>1 | 0 / 7 (0.00%)<br>0  |
| Eye disorders<br>BLURRED VISION<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                             | Additional description: BLURRED VISION                               |                     |                     |
|                                                                                                                                                                                | 0 / 3 (0.00%)<br>0                                                   | 0 / 3 (0.00%)<br>0  | 2 / 7 (28.57%)<br>2 |
| EYE DISORDERS - OTHER, SPECIFY<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                              | Additional description: EYE DISORDERS - OTHER, SPECIFY               |                     |                     |
|                                                                                                                                                                                | 0 / 3 (0.00%)<br>0                                                   | 0 / 3 (0.00%)<br>0  | 0 / 7 (0.00%)<br>0  |
| Gastrointestinal disorders<br>ABDOMINAL PAIN<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                | Additional description: ABDOMINAL PAIN                               |                     |                     |
|                                                                                                                                                                                | 0 / 3 (0.00%)<br>0                                                   | 0 / 3 (0.00%)<br>0  | 1 / 7 (14.29%)<br>1 |
| BLOATING<br>alternative assessment type: Non-systematic                                                                                                                        | Additional description: BLOATING                                     |                     |                     |
|                                                                                                                                                                                |                                                                      |                     |                     |

|                                             |                                                                     |                |                |
|---------------------------------------------|---------------------------------------------------------------------|----------------|----------------|
| subjects affected / exposed                 | 0 / 3 (0.00%)                                                       | 0 / 3 (0.00%)  | 1 / 7 (14.29%) |
| occurrences (all)                           | 0                                                                   | 0              | 1              |
| CONSTIPATION                                | Additional description: CONSTIPATION                                |                |                |
| alternative assessment type: Non-systematic |                                                                     |                |                |
| subjects affected / exposed                 | 1 / 3 (33.33%)                                                      | 1 / 3 (33.33%) | 2 / 7 (28.57%) |
| occurrences (all)                           | 1                                                                   | 1              | 8              |
| DIARRHEA                                    | Additional description: DIARRHEA                                    |                |                |
| alternative assessment type: Non-systematic |                                                                     |                |                |
| subjects affected / exposed                 | 2 / 3 (66.67%)                                                      | 2 / 3 (66.67%) | 6 / 7 (85.71%) |
| occurrences (all)                           | 44                                                                  | 6              | 28             |
| DYSPEPSIA                                   | Additional description: DYSPEPSIA                                   |                |                |
| alternative assessment type: Non-systematic |                                                                     |                |                |
| subjects affected / exposed                 | 1 / 3 (33.33%)                                                      | 0 / 3 (0.00%)  | 0 / 7 (0.00%)  |
| occurrences (all)                           | 1                                                                   | 0              | 0              |
| GASTROINTESTINAL DISORDERS - OTHER, SPECIFY | Additional description: GASTROINTESTINAL DISORDERS - OTHER, SPECIFY |                |                |
| alternative assessment type: Non-systematic |                                                                     |                |                |
| subjects affected / exposed                 | 0 / 3 (0.00%)                                                       | 2 / 3 (66.67%) | 1 / 7 (14.29%) |
| occurrences (all)                           | 0                                                                   | 3              | 1              |
| GASTROINTESTINAL PAIN                       | Additional description: GASTROINTESTINAL PAIN                       |                |                |
| alternative assessment type: Non-systematic |                                                                     |                |                |
| subjects affected / exposed                 | 0 / 3 (0.00%)                                                       | 0 / 3 (0.00%)  | 0 / 7 (0.00%)  |
| occurrences (all)                           | 0                                                                   | 0              | 0              |
| MUCOSITIS ORAL                              | Additional description: MUCOSITIS ORAL                              |                |                |
| alternative assessment type: Non-systematic |                                                                     |                |                |
| subjects affected / exposed                 | 0 / 3 (0.00%)                                                       | 0 / 3 (0.00%)  | 0 / 7 (0.00%)  |
| occurrences (all)                           | 0                                                                   | 0              | 0              |
| NAUSEA                                      | Additional description: NAUSEA                                      |                |                |
| alternative assessment type: Non-systematic |                                                                     |                |                |
| subjects affected / exposed                 | 3 / 3 (100.00%)                                                     | 2 / 3 (66.67%) | 6 / 7 (85.71%) |
| occurrences (all)                           | 30                                                                  | 3              | 32             |
| ORAL PAIN                                   | Additional description: ORAL PAIN                                   |                |                |
| alternative assessment type: Non-systematic |                                                                     |                |                |
| subjects affected / exposed                 | 0 / 3 (0.00%)                                                       | 0 / 3 (0.00%)  | 0 / 7 (0.00%)  |
| occurrences (all)                           | 0                                                                   | 0              | 0              |

|                                                                                                                                                                       |                                                                                 |                     |                     |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|---------------------|---------------------|
| <b>SALIVARY DUCT INFLAMMATION</b><br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                  | Additional description: SALIVARY DUCT INFLAMMATION                              |                     |                     |
|                                                                                                                                                                       | 1 / 3 (33.33%)<br>4                                                             | 0 / 3 (0.00%)<br>0  | 0 / 7 (0.00%)<br>0  |
|                                                                                                                                                                       |                                                                                 |                     |                     |
| <b>STOMACH PAIN</b><br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                                | Additional description: STOMACH PAIN                                            |                     |                     |
|                                                                                                                                                                       | 0 / 3 (0.00%)<br>0                                                              | 1 / 3 (33.33%)<br>2 | 0 / 7 (0.00%)<br>0  |
|                                                                                                                                                                       |                                                                                 |                     |                     |
| <b>VOMITING</b><br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                                    | Additional description: VOMITING                                                |                     |                     |
|                                                                                                                                                                       | 1 / 3 (33.33%)<br>1                                                             | 2 / 3 (66.67%)<br>2 | 5 / 7 (71.43%)<br>8 |
|                                                                                                                                                                       |                                                                                 |                     |                     |
| <b>Skin and subcutaneous tissue disorders</b><br><b>DRY SKIN</b><br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)   | Additional description: DRY SKIN                                                |                     |                     |
|                                                                                                                                                                       | 1 / 3 (33.33%)<br>1                                                             | 0 / 3 (0.00%)<br>0  | 0 / 7 (0.00%)<br>0  |
|                                                                                                                                                                       |                                                                                 |                     |                     |
| <b>RASH MACULO-PAPULAR</b><br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                         | Additional description: RASH MACULO-PAPULAR                                     |                     |                     |
|                                                                                                                                                                       | 0 / 3 (0.00%)<br>0                                                              | 0 / 3 (0.00%)<br>0  | 0 / 7 (0.00%)<br>0  |
|                                                                                                                                                                       |                                                                                 |                     |                     |
| <b>SCALP PAIN</b><br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                                  | Additional description: SCALP PAIN                                              |                     |                     |
|                                                                                                                                                                       | 0 / 3 (0.00%)<br>0                                                              | 0 / 3 (0.00%)<br>0  | 0 / 7 (0.00%)<br>0  |
|                                                                                                                                                                       |                                                                                 |                     |                     |
| <b>SKIN AND SUBCUTANEOUS TISSUE DISORDERS - OTHER, SPECIFY</b><br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)     | Additional description: SKIN AND SUBCUTANEOUS TISSUE DISORDERS - OTHER, SPECIFY |                     |                     |
|                                                                                                                                                                       | 0 / 3 (0.00%)<br>0                                                              | 1 / 3 (33.33%)<br>3 | 1 / 7 (14.29%)<br>2 |
|                                                                                                                                                                       |                                                                                 |                     |                     |
| <b>Renal and urinary disorders</b><br><b>CYSTITIS NONINFECTIVE</b><br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | Additional description: CYSTITIS NONINFECTIVE                                   |                     |                     |
|                                                                                                                                                                       | 1 / 3 (33.33%)<br>2                                                             | 0 / 3 (0.00%)<br>0  | 1 / 7 (14.29%)<br>3 |
|                                                                                                                                                                       |                                                                                 |                     |                     |
| <b>HEMATURIA</b>                                                                                                                                                      | Additional description: HEMATURIA                                               |                     |                     |
|                                                                                                                                                                       |                                                                                 |                     |                     |

|                                                                                                 |                                                                      |                     |                     |
|-------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|---------------------|---------------------|
| alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 2 / 3 (66.67%)<br>5                                                  | 0 / 3 (0.00%)<br>0  | 1 / 7 (14.29%)<br>1 |
| RENAL AND URINARY DISORDERS - OTHER, SPECIFY                                                    | Additional description: RENAL AND URINARY DISORDERS - OTHER, SPECIFY |                     |                     |
| alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0                                                   | 0 / 3 (0.00%)<br>0  | 2 / 7 (28.57%)<br>2 |
| URINARY FREQUENCY                                                                               | Additional description: URINARY FREQUENCY                            |                     |                     |
| alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0                                                   | 0 / 3 (0.00%)<br>0  | 2 / 7 (28.57%)<br>2 |
| URINARY RETENTION                                                                               | Additional description: URINARY RETENTION                            |                     |                     |
| alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 1 / 3 (33.33%)<br>1                                                  | 0 / 3 (0.00%)<br>0  | 1 / 7 (14.29%)<br>1 |
| Musculoskeletal and connective tissue disorders                                                 |                                                                      |                     |                     |
| BACK PAIN                                                                                       | Additional description: BACK PAIN                                    |                     |                     |
| alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0                                                   | 2 / 3 (66.67%)<br>2 | 3 / 7 (42.86%)<br>4 |
| BONE PAIN                                                                                       | Additional description: BONE PAIN                                    |                     |                     |
| alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0                                                   | 1 / 3 (33.33%)<br>1 | 1 / 7 (14.29%)<br>1 |
| BUTTOCK PAIN                                                                                    | Additional description: BUTTOCK PAIN                                 |                     |                     |
| alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0                                                   | 0 / 3 (0.00%)<br>0  | 0 / 7 (0.00%)<br>0  |
| CHEST WALL PAIN                                                                                 | Additional description: CHEST WALL PAIN                              |                     |                     |
| alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0                                                   | 1 / 3 (33.33%)<br>2 | 0 / 7 (0.00%)<br>0  |
| FLANK PAIN                                                                                      | Additional description: FLANK PAIN                                   |                     |                     |
| alternative assessment type: Non-systematic                                                     |                                                                      |                     |                     |



|                                                                 |                                                                                         |                |                |
|-----------------------------------------------------------------|-----------------------------------------------------------------------------------------|----------------|----------------|
| subjects affected / exposed                                     | 1 / 3 (33.33%)                                                                          | 0 / 3 (0.00%)  | 2 / 7 (28.57%) |
| occurrences (all)                                               | 1                                                                                       | 0              | 3              |
| MUSCLE WEAKNESS LOWER LIMB                                      | Additional description: MUSCLE WEAKNESS LOWER LIMB                                      |                |                |
| alternative assessment type: Non-systematic                     |                                                                                         |                |                |
| subjects affected / exposed                                     | 0 / 3 (0.00%)                                                                           | 0 / 3 (0.00%)  | 1 / 7 (14.29%) |
| occurrences (all)                                               | 0                                                                                       | 0              | 1              |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDER - OTHER, SPECIFY | Additional description: MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDER - OTHER, SPECIFY |                |                |
| alternative assessment type: Non-systematic                     |                                                                                         |                |                |
| subjects affected / exposed                                     | 1 / 3 (33.33%)                                                                          | 1 / 3 (33.33%) | 2 / 7 (28.57%) |
| occurrences (all)                                               | 1                                                                                       | 6              | 3              |
| NECK PAIN                                                       | Additional description: NECK PAIN                                                       |                |                |
| alternative assessment type: Non-systematic                     |                                                                                         |                |                |
| subjects affected / exposed                                     | 0 / 3 (0.00%)                                                                           | 0 / 3 (0.00%)  | 1 / 7 (14.29%) |
| occurrences (all)                                               | 0                                                                                       | 0              | 1              |
| Infections and infestations                                     |                                                                                         |                |                |
| BLADDER INFECTION                                               | Additional description: BLADDER INFECTION                                               |                |                |
| alternative assessment type: Non-systematic                     |                                                                                         |                |                |
| subjects affected / exposed                                     | 0 / 3 (0.00%)                                                                           | 0 / 3 (0.00%)  | 1 / 7 (14.29%) |
| occurrences (all)                                               | 0                                                                                       | 0              | 2              |
| INFECTIONS AND INFESTATIONS - OTHER, SPECIFY                    | Additional description: INFECTIONS AND INFESTATIONS - OTHER, SPECIFY                    |                |                |
| alternative assessment type: Non-systematic                     |                                                                                         |                |                |
| subjects affected / exposed                                     | 2 / 3 (66.67%)                                                                          | 2 / 3 (66.67%) | 2 / 7 (28.57%) |
| occurrences (all)                                               | 6                                                                                       | 4              | 2              |
| LARYNGITIS                                                      | Additional description: LARYNGITIS                                                      |                |                |
| alternative assessment type: Non-systematic                     |                                                                                         |                |                |
| subjects affected / exposed                                     | 0 / 3 (0.00%)                                                                           | 1 / 3 (33.33%) | 0 / 7 (0.00%)  |
| occurrences (all)                                               | 0                                                                                       | 1              | 0              |
| LUNG INFECTION                                                  | Additional description: LUNG INFECTION                                                  |                |                |
| alternative assessment type: Non-systematic                     |                                                                                         |                |                |
| subjects affected / exposed                                     | 0 / 3 (0.00%)                                                                           | 0 / 3 (0.00%)  | 0 / 7 (0.00%)  |
| occurrences (all)                                               | 0                                                                                       | 0              | 0              |
| PENILE INFECTION                                                | Additional description: PENILE INFECTION                                                |                |                |
| alternative assessment type: Non-systematic                     |                                                                                         |                |                |

|                                             |                                                     |                |                |
|---------------------------------------------|-----------------------------------------------------|----------------|----------------|
| subjects affected / exposed                 | 0 / 3 (0.00%)                                       | 0 / 3 (0.00%)  | 1 / 7 (14.29%) |
| occurrences (all)                           | 0                                                   | 0              | 2              |
| PHARYNGITIS                                 | Additional description: PHARYNGITIS                 |                |                |
| alternative assessment type: Non-systematic |                                                     |                |                |
| subjects affected / exposed                 | 0 / 3 (0.00%)                                       | 1 / 3 (33.33%) | 0 / 7 (0.00%)  |
| occurrences (all)                           | 0                                                   | 1              | 0              |
| RHINITIS INFECTIVE                          | Additional description: RHINITIS INFECTIVE          |                |                |
| alternative assessment type: Non-systematic |                                                     |                |                |
| subjects affected / exposed                 | 1 / 3 (33.33%)                                      | 0 / 3 (0.00%)  | 0 / 7 (0.00%)  |
| occurrences (all)                           | 6                                                   | 0              | 0              |
| SINUSITIS                                   | Additional description: SINUSITIS                   |                |                |
| alternative assessment type: Non-systematic |                                                     |                |                |
| subjects affected / exposed                 | 0 / 3 (0.00%)                                       | 0 / 3 (0.00%)  | 1 / 7 (14.29%) |
| occurrences (all)                           | 0                                                   | 0              | 2              |
| SKIN INFECTION                              | Additional description: SKIN INFECTION              |                |                |
| alternative assessment type: Non-systematic |                                                     |                |                |
| subjects affected / exposed                 | 0 / 3 (0.00%)                                       | 0 / 3 (0.00%)  | 1 / 7 (14.29%) |
| occurrences (all)                           | 0                                                   | 0              | 1              |
| SOFT TISSUE INFECTION                       | Additional description: SOFT TISSUE INFECTION       |                |                |
| alternative assessment type: Non-systematic |                                                     |                |                |
| subjects affected / exposed                 | 0 / 3 (0.00%)                                       | 0 / 3 (0.00%)  | 1 / 7 (14.29%) |
| occurrences (all)                           | 0                                                   | 0              | 1              |
| UPPER RESPIRATORY INFECTION                 | Additional description: UPPER RESPIRATORY INFECTION |                |                |
| alternative assessment type: Non-systematic |                                                     |                |                |
| subjects affected / exposed                 | 2 / 3 (66.67%)                                      | 0 / 3 (0.00%)  | 1 / 7 (14.29%) |
| occurrences (all)                           | 2                                                   | 0              | 1              |
| URINARY TRACT INFECTION                     | Additional description: URINARY TRACT INFECTION     |                |                |
| alternative assessment type: Non-systematic |                                                     |                |                |
| subjects affected / exposed                 | 1 / 3 (33.33%)                                      | 0 / 3 (0.00%)  | 1 / 7 (14.29%) |
| occurrences (all)                           | 1                                                   | 0              | 2              |
| UTERINE INFECTION                           | Additional description: UTERINE INFECTION           |                |                |
| alternative assessment type: Non-systematic |                                                     |                |                |
| subjects affected / exposed                 | 0 / 3 (0.00%)                                       | 0 / 3 (0.00%)  | 0 / 7 (0.00%)  |
| occurrences (all)                           | 0                                                   | 0              | 0              |

|                                             |                                       |                |                |
|---------------------------------------------|---------------------------------------|----------------|----------------|
| Metabolism and nutrition disorders          |                                       |                |                |
| ANOREXIA                                    | Additional description: ANOREXIA      |                |                |
| alternative assessment type: Non-systematic |                                       |                |                |
| subjects affected / exposed                 | 1 / 3 (33.33%)                        | 1 / 3 (33.33%) | 2 / 7 (28.57%) |
| occurrences (all)                           | 8                                     | 2              | 7              |
| DEHYDRATION                                 | Additional description: DEHYDRATION   |                |                |
| alternative assessment type: Non-systematic |                                       |                |                |
| subjects affected / exposed                 | 0 / 3 (0.00%)                         | 0 / 3 (0.00%)  | 0 / 7 (0.00%)  |
| occurrences (all)                           | 0                                     | 0              | 0              |
| HYPERGLYCEMIA                               | Additional description: HYPERGLYCEMIA |                |                |
| alternative assessment type: Non-systematic |                                       |                |                |
| subjects affected / exposed                 | 0 / 3 (0.00%)                         | 1 / 3 (33.33%) | 0 / 7 (0.00%)  |
| occurrences (all)                           | 0                                     | 1              | 0              |
| HYPOCALCEMIA                                | Additional description: HYPOCALCEMIA  |                |                |
| alternative assessment type: Non-systematic |                                       |                |                |
| subjects affected / exposed                 | 0 / 3 (0.00%)                         | 1 / 3 (33.33%) | 1 / 7 (14.29%) |
| occurrences (all)                           | 0                                     | 1              | 2              |
| HYPOGLYCEMIA                                | Additional description: HYPOGLYCEMIA  |                |                |
| alternative assessment type: Non-systematic |                                       |                |                |
| subjects affected / exposed                 | 0 / 3 (0.00%)                         | 0 / 3 (0.00%)  | 1 / 7 (14.29%) |
| occurrences (all)                           | 0                                     | 0              | 2              |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date          | Amendment                                                                                                                                                                                                                                                                                       |
|---------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 29 April 2015 | Protocol updated with details of intermediate dose levels to be explored, if required, during the Phase I component of the study. Clarification of the PK requirements for Phase I patients, including timings and the removal of the Day -7 single dose for PK testing from cohort 1* onwards. |
| 04 April 2016 | Protocol updated with the addition of enzalutamide as an IMP for the study. As a result of this update, an additional Phase I cohort exploring the combination of idasanutlin (RO5503781) and enzalutamide included in the study protocol.                                                      |
| 26 June 2017  | Notification that the Phase II component of the study no longer supported by our partner and therefore would not be proceeding. Additionally, clarification provided around the allowed window for study assessments and visits.                                                                |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported