



## Clinical trial results:

### The [PEARL] Study : Pet imaging as a biomarker of Everolimus Added value in hormone Refractory postmenopausal women

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2012-004860-22 |
| Trial protocol           | BE             |
| Global end of trial date | 06 July 2021   |

#### Results information

|                                   |                                                            |
|-----------------------------------|------------------------------------------------------------|
| Result version number             | v1 (current)                                               |
| This version publication date     | 15 December 2022                                           |
| First version publication date    | 15 December 2022                                           |
| Summary attachment (see zip file) | PEARL_final_report (2012-004860-22-Final_study_report.pdf) |

#### Trial information

##### Trial identification

|                       |                   |
|-----------------------|-------------------|
| Sponsor protocol code | IJB-BCTL:20120306 |
|-----------------------|-------------------|

##### Additional study identifiers

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

Notes:

#### Sponsors

|                              |                                                                                     |
|------------------------------|-------------------------------------------------------------------------------------|
| Sponsor organisation name    | Institut Jules Bordet                                                               |
| Sponsor organisation address | Rue Meylemeersch,90, Brussels, Belgium, 1070                                        |
| Public contact               | Andrea Gombos, institut Jules Bordet, 32 2541 7232, andrea.gombos@bordet.be         |
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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 August 2021 |
| Is this the analysis of the primary completion data? | No             |
| Global end of trial reached?                         | Yes            |
| Global end of trial date                             | 06 July 2021   |
| Was the trial ended prematurely?                     | No             |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate if early metabolic response (MR) using FDG-PET/CT is associated with progression free survival (PFS) in ER+, HER2 negative ABC or MBC patients treated with exemestane plus everolimus.

Protection of trial subjects:

insurance

Background therapy: -

Evidence for comparator: -

|                                                           |                 |
|-----------------------------------------------------------|-----------------|
| Actual start date of recruitment                          | 15 January 2014 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | No              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |             |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Belgium: 64 |
| Worldwide total number of subjects   | 64          |
| EEA total number of subjects         | 64          |

Notes:

### Subjects enrolled per age group

|                                           |    |
|-------------------------------------------|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 51 |
| From 65 to 84 years                       | 13 |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Belgium

pilot phase - inclusion of patients from February 2014 till June 2016

main phase - inclusion of patients from June 2017 till May 2018

### Pre-assignment

Screening details:

Screening assessments to confirm eligibility must be performed prior to the first dose of studydrug.

Physical examination including performance status, height and weight must be performed within 21 days prior to the first dose of study treatment.

### Period 1

|                              |                       |
|------------------------------|-----------------------|
| Period 1 title               | Pilot and main phases |
| Is this the baseline period? | No                    |
| Allocation method            | Not applicable        |
| Blinding used                | Not blinded           |

### Arms

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

Arm description: -

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

Dosage and administration details:

5.0 mg and 10 mg strength for oral administration

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

Dosage and administration details:

25 mg strength for oral administration

|                  |             |
|------------------|-------------|
| <b>Arm title</b> | Pilot phase |
|------------------|-------------|

Arm description: -

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

Dosage and administration details:

5.0 mg and 10 mg strength for oral administration

|                                        |            |
|----------------------------------------|------------|
| Investigational medicinal product name | Exemestane |
| Investigational medicinal product code |            |
| Other name                             |            |

|                          |          |
|--------------------------|----------|
| Pharmaceutical forms     | Tablet   |
| Routes of administration | Oral use |

Dosage and administration details:

25 mg strength for oral administration

| Number of subjects in period 1   | Main phase | Pilot phase |
|----------------------------------|------------|-------------|
| Started                          | 20         | 44          |
| Completed                        | 20         | 27          |
| Not completed                    | 0          | 17          |
| increase of liver function tests | -          | 1           |
| not evaluable for PET            | -          | 6           |
| HER2+ on baseline biopsy         | -          | 2           |
| no PET measurable lesion         | -          | 8           |

## Period 2

|                              |                          |
|------------------------------|--------------------------|
| Period 2 title               | Evaluable subjects (ITT) |
| Is this the baseline period? | Yes <sup>[1]</sup>       |
| Allocation method            | Not applicable           |
| Blinding used                | Not blinded              |

## Arms

|                                                   |                          |
|---------------------------------------------------|--------------------------|
| Arm title                                         | Evaluable subjects (ITT) |
| Arm description: -                                |                          |
| Arm type                                          | Experimental             |
| Investigational medicinal product name            | Everolimus               |
| Investigational medicinal product code            |                          |
| Other name                                        |                          |
| Pharmaceutical forms                              | Tablet                   |
| Routes of administration                          | Oral use                 |
| Dosage and administration details:                |                          |
| 5.0 mg and 10 mg strength for oral administration |                          |
| Investigational medicinal product name            | Exemestane               |
| Investigational medicinal product code            |                          |
| Other name                                        |                          |
| Pharmaceutical forms                              | Tablet                   |
| Routes of administration                          | Oral use                 |

Dosage and administration details:

25 mg strength for oral administration

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Notes:

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

Justification: Baseline characteristics are provided for evaluable subjects.

| <b>Number of subjects in period 2<sup>[2]</sup></b> | Evaluable subjects (ITT) |
|-----------------------------------------------------|--------------------------|
| Started                                             | 47                       |
| Completed                                           | 47                       |

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Notes:

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

Justification: Analyzes have been performed on evaluable subjects.

## Baseline characteristics

### Reporting groups

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Evaluable subjects (ITT) |
|-----------------------|--------------------------|

Reporting group description: -

| Reporting group values | Evaluable subjects (ITT) | Total |  |
|------------------------|--------------------------|-------|--|
| Number of subjects     | 47                       | 47    |  |
| Age categorical        |                          |       |  |
| Units: Subjects        |                          |       |  |

|                          |        |    |  |
|--------------------------|--------|----|--|
| Age continuous           |        |    |  |
| Units: years             |        |    |  |
| arithmetic mean          | 57.1   |    |  |
| standard deviation       | ± 13.4 | -  |  |
| Gender categorical       |        |    |  |
| Units: Subjects          |        |    |  |
| Female                   | 47     | 47 |  |
| Male                     | 0      | 0  |  |
| ECOG PS                  |        |    |  |
| Units: Subjects          |        |    |  |
| Zero                     | 23     | 23 |  |
| One                      | 23     | 23 |  |
| Two                      | 1      | 1  |  |
| Histology                |        |    |  |
| Units: Subjects          |        |    |  |
| Invasive ductal          | 38     | 38 |  |
| Invasive lobular         | 8      | 8  |  |
| Unknown                  | 1      | 1  |  |
| Grade                    |        |    |  |
| Units: Subjects          |        |    |  |
| G1                       | 8      | 8  |  |
| G2                       | 17     | 17 |  |
| G3                       | 11     | 11 |  |
| Unknown                  | 11     | 11 |  |
| Current disease status   |        |    |  |
| Units: Subjects          |        |    |  |
| Metastatic               | 45     | 45 |  |
| Locally advanced         | 2      | 2  |  |
| Current disease status   |        |    |  |
| Units: Subjects          |        |    |  |
| Metastatic Lung or liver | 35     | 35 |  |
| Metastatic Bone only     | 6      | 6  |  |
| Metastatic Other         | 4      | 4  |  |
| Locally advanced         | 2      | 2  |  |
| N Metastatic sites       |        |    |  |
| Units: Subjects          |        |    |  |
| Zero                     | 2      | 2  |  |

|                                                                                                              |    |    |  |
|--------------------------------------------------------------------------------------------------------------|----|----|--|
| 12                                                                                                           | 24 | 24 |  |
| ≥3                                                                                                           | 21 | 21 |  |
| KI67 (primary)<br>Units: Subjects                                                                            |    |    |  |
| <10%                                                                                                         | 5  | 5  |  |
| 10%15%                                                                                                       | 6  | 6  |  |
| 16%25%                                                                                                       | 9  | 9  |  |
| >25%                                                                                                         | 17 | 17 |  |
| Unknown                                                                                                      | 10 | 10 |  |
| Prior CDK 4/6<br>Units: Subjects                                                                             |    |    |  |
| No                                                                                                           | 35 | 35 |  |
| Yes                                                                                                          | 12 | 12 |  |
| Number of lines CT in advanced setting<br>Units: Subjects                                                    |    |    |  |
| Zero                                                                                                         | 20 | 20 |  |
| One                                                                                                          | 14 | 14 |  |
| ≥2                                                                                                           | 13 | 13 |  |
| Number of lines ET in advanced setting<br>Units: Subjects                                                    |    |    |  |
| Zero                                                                                                         | 2  | 2  |  |
| One                                                                                                          | 13 | 13 |  |
| ≥2                                                                                                           | 32 | 32 |  |
| NSAI sensitive<br>Units: Subjects                                                                            |    |    |  |
| No                                                                                                           | 13 | 13 |  |
| Yes                                                                                                          | 34 | 34 |  |
| Subjects who continued exemestane<br>after having stopped everolimus<br>Units: Subjects                      |    |    |  |
| Yes                                                                                                          | 13 | 13 |  |
| No                                                                                                           | 34 | 34 |  |
| Subjects who continued exemestane<br>more than a month after having stopped<br>everolimus<br>Units: Subjects |    |    |  |
| Yes                                                                                                          | 5  | 5  |  |
| No                                                                                                           | 42 | 42 |  |
| Subjects with treatment interruption of<br>exemestane (protocol violation)<br>Units: Subjects                |    |    |  |
| Yes                                                                                                          | 1  | 1  |  |
| No                                                                                                           | 46 | 46 |  |
| Subjects with treatment interruption<br>everolimus<br>Units: Subjects                                        |    |    |  |
| Yes                                                                                                          | 23 | 23 |  |
| No                                                                                                           | 24 | 24 |  |
| Subjects with dose reduction everolimus<br>(from 10 till 5)<br>Units: Subjects                               |    |    |  |
| Yes                                                                                                          | 21 | 21 |  |
| No                                                                                                           | 26 | 26 |  |

|                                                                  |           |    |  |
|------------------------------------------------------------------|-----------|----|--|
| Days between baseline PET and start treatment<br>Units: Subjects |           |    |  |
| 1 - 7 days                                                       | 36        | 36 |  |
| 8-14 days                                                        | 9         | 9  |  |
| ≥15 days                                                         | 2         | 2  |  |
| Days between start treatment and PET D14<br>Units: Subjects      |           |    |  |
| 12                                                               | 2         | 2  |  |
| 13                                                               | 5         | 5  |  |
| 14                                                               | 32        | 32 |  |
| 15                                                               | 6         | 6  |  |
| 16                                                               | 1         | 1  |  |
| 17                                                               | 1         | 1  |  |
| Duration everolimus treatment                                    |           |    |  |
| (=from start everolimus till last day everolimus)                |           |    |  |
| Units: months                                                    |           |    |  |
| arithmetic mean                                                  | 5.5       |    |  |
| standard deviation                                               | ± 5.2     | -  |  |
| Duration everolimus treatment                                    |           |    |  |
| (=from start everolimus till last day everolimus)                |           |    |  |
| Units: months                                                    |           |    |  |
| median                                                           | 4.1       |    |  |
| full range (min-max)                                             | 1 to 29   | -  |  |
| Duration exemestane treatment                                    |           |    |  |
| (= from start exemestane till last day exemestane )              |           |    |  |
| Units: months                                                    |           |    |  |
| arithmetic mean                                                  | 6.2       |    |  |
| standard deviation                                               | ± 5.5     | -  |  |
| Duration exemestane treatment (in months)                        |           |    |  |
| (= from start exemestane till last day exemestane )              |           |    |  |
| Units: months                                                    |           |    |  |
| median                                                           | 5         |    |  |
| full range (min-max)                                             | 1.6 to 29 | -  |  |



## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                   |                                                          |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|
| Reporting group title                                                                                                                                                                                                                                             | Main phase                                               |
| Reporting group description: -                                                                                                                                                                                                                                    |                                                          |
| Reporting group title                                                                                                                                                                                                                                             | Pilot phase                                              |
| Reporting group description: -                                                                                                                                                                                                                                    |                                                          |
| Reporting group title                                                                                                                                                                                                                                             | Evaluable subjects (ITT)                                 |
| Reporting group description: -                                                                                                                                                                                                                                    |                                                          |
| Subject analysis set title                                                                                                                                                                                                                                        | F-FDG-PET/CT response on D14 Consist 25%                 |
| Subject analysis set type                                                                                                                                                                                                                                         | Per protocol                                             |
| Subject analysis set description:<br>subjects with a SUVmax reduction of more than 25% in all lesions classified as responders                                                                                                                                    |                                                          |
| Subject analysis set title                                                                                                                                                                                                                                        | F-FDG-PET/CT non-response on D14 Consist 25%             |
| Subject analysis set type                                                                                                                                                                                                                                         | Per protocol                                             |
| Subject analysis set description:<br>subjects with a SUVmax reduction of less than or equal to 25% in all lesions classified as responders                                                                                                                        |                                                          |
| Subject analysis set title                                                                                                                                                                                                                                        | F-FDG-PET/CT response on D14 Consist 15%("post-hoc")     |
| Subject analysis set type                                                                                                                                                                                                                                         | Sub-group analysis                                       |
| Subject analysis set description:<br>Subjects with a > 15 % homogenous decrease in maximum standardized uptake value (SUVmax) in all target lesions are considered as "responders". This is a "post-hoc" analysis, initially not scheduled by the study protocol. |                                                          |
| Subject analysis set title                                                                                                                                                                                                                                        | F-FDG-PET/CT non-response on D14 Consist 15%("post-hoc") |
| Subject analysis set type                                                                                                                                                                                                                                         | Sub-group analysis                                       |
| Subject analysis set description:<br>Subjects with a > 15 % homogenous decrease in maximum standardized uptake value (SUVmax) in all target lesions are considered as "responders". This is a "post-hoc" analysis, initially not scheduled by the study protocol. |                                                          |

### Primary: Time to progression

|                                                                                         |                     |
|-----------------------------------------------------------------------------------------|---------------------|
| End point title                                                                         | Time to progression |
| End point description:                                                                  |                     |
|                                                                                         |                     |
| End point type                                                                          | Primary             |
| End point timeframe:                                                                    |                     |
| Time to progression since date of early PET, in order to adjust for guarantee-time bias |                     |

| End point values                      | F-FDG-PET/CT response on D14 Consist 25% | F-FDG-PET/CT non-response on D14 Consist 25% | F-FDG-PET/CT response on D14 Consist 15%("post-hoc") | F-FDG-PET/CT non-response on D14 Consist 15%("post-hoc") |
|---------------------------------------|------------------------------------------|----------------------------------------------|------------------------------------------------------|----------------------------------------------------------|
| Subject group type                    | Subject analysis set                     | Subject analysis set                         | Subject analysis set                                 | Subject analysis set                                     |
| Number of subjects analysed           | 15                                       | 30                                           | 23                                                   | 22                                                       |
| Units: months                         |                                          |                                              |                                                      |                                                          |
| median (inter-quartile range (Q1-Q3)) | 6 (4.6 to 13.9)                          | 3.1 (2.3 to 5.5)                             | 6.4 (2.9 to 13.9)                                    | 2.2 (1.9 to 4.9)                                         |

|                                   |                                                                                                      |
|-----------------------------------|------------------------------------------------------------------------------------------------------|
| <b>Attachments (see zip file)</b> | Kaplan–Meier plots/41523_2021_331_Fig1_HTML.jpeg<br>Impact of variables on PFS (univariate analysis) |
|-----------------------------------|------------------------------------------------------------------------------------------------------|

## Statistical analyses

|                                                                                                                                                                                 |                                                                                         |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                               | PFS according to PET scan Consist 25% on D14                                            |
| Statistical analysis description:<br>subjects with > 25% homogenous decrease in maximum standardized uptake value (SUVmax) in all target lesions are considered as "responders" |                                                                                         |
| Comparison groups                                                                                                                                                               | F-FDG-PET/CT response on D14 Consist 25% v F-FDG-PET/CT non-response on D14 Consist 25% |
| Number of subjects included in analysis                                                                                                                                         | 45                                                                                      |
| Analysis specification                                                                                                                                                          | Pre-specified                                                                           |
| Analysis type                                                                                                                                                                   | other                                                                                   |
| P-value                                                                                                                                                                         | = 0.44                                                                                  |
| Method                                                                                                                                                                          | Logrank                                                                                 |
| Parameter estimate                                                                                                                                                              | Hazard ratio (HR)                                                                       |
| Point estimate                                                                                                                                                                  | 0.77                                                                                    |
| Confidence interval                                                                                                                                                             |                                                                                         |
| level                                                                                                                                                                           | 95 %                                                                                    |
| sides                                                                                                                                                                           | 2-sided                                                                                 |
| lower limit                                                                                                                                                                     | 0.4                                                                                     |
| upper limit                                                                                                                                                                     | 1.5                                                                                     |

|                                         |                                                                                                                 |
|-----------------------------------------|-----------------------------------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | PFS according to PET scan Consist 15% on D14                                                                    |
| Comparison groups                       | F-FDG-PET/CT response on D14 Consist 15%("post-hoc") v F-FDG-PET/CT non-response on D14 Consist 15%("post-hoc") |
| Number of subjects included in analysis | 45                                                                                                              |
| Analysis specification                  | Post-hoc                                                                                                        |
| Analysis type                           | other                                                                                                           |
| P-value                                 | = 0.0032                                                                                                        |
| Method                                  | Logrank                                                                                                         |
| Parameter estimate                      | Hazard ratio (HR)                                                                                               |
| Point estimate                          | 0.38                                                                                                            |
| Confidence interval                     |                                                                                                                 |
| level                                   | 95 %                                                                                                            |
| sides                                   | 2-sided                                                                                                         |
| lower limit                             | 0.2                                                                                                             |
| upper limit                             | 0.72                                                                                                            |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (SAEs) and non-serious adverse events (AEs) were collected from the first administration of study treatments until 28 days after the last dose of study treatments.

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

### Dictionary used

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

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

### Reporting groups

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Safety analysis |
|-----------------------|-----------------|

Reporting group description:

Progression of underlying malignancy is not reported as an AE if it was clearly consistent with the suspected progression of the underlying cancer. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as an SAE/AE. Clinical symptoms of progression may be reported as AEs or SAEs if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study. If there is any uncertainty about an AE being due to the disease under study, it should be reported as an AE or SAE. Clinical symptoms of underlying malignancy, even if they meet a seriousness criteria, should not be reported as SAE unless the investigator considers them as more severe than expected.

| Serious adverse events                            | Safety analysis |  |  |
|---------------------------------------------------|-----------------|--|--|
| Total subjects affected by serious adverse events |                 |  |  |
| subjects affected / exposed                       | 9 / 55 (16.36%) |  |  |
| number of deaths (all causes)                     | 4               |  |  |
| number of deaths resulting from adverse events    | 1               |  |  |
| Cardiac disorders                                 |                 |  |  |
| Cardiac failure                                   |                 |  |  |
| subjects affected / exposed                       | 1 / 55 (1.82%)  |  |  |
| occurrences causally related to treatment / all   | 0 / 1           |  |  |
| deaths causally related to treatment / all        | 0 / 0           |  |  |
| Myocardial ischaemia                              |                 |  |  |
| subjects affected / exposed                       | 1 / 55 (1.82%)  |  |  |
| occurrences causally related to treatment / all   | 1 / 1           |  |  |
| deaths causally related to treatment / all        | 0 / 0           |  |  |
| Blood and lymphatic system disorders              |                 |  |  |
| Febrile neutropenia                               |                 |  |  |
| subjects affected / exposed                       | 1 / 55 (1.82%)  |  |  |
| occurrences causally related to treatment / all   | 0 / 1           |  |  |
| deaths causally related to treatment / all        | 0 / 0           |  |  |

|                                                      |                |  |  |
|------------------------------------------------------|----------------|--|--|
| General disorders and administration site conditions |                |  |  |
| Mucosal inflammation                                 |                |  |  |
| subjects affected / exposed                          | 1 / 55 (1.82%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Gastrointestinal disorders                           |                |  |  |
| Abdominal pain                                       |                |  |  |
| subjects affected / exposed                          | 1 / 55 (1.82%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Diarrhoea                                            |                |  |  |
| subjects affected / exposed                          | 1 / 55 (1.82%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Nausea                                               |                |  |  |
| subjects affected / exposed                          | 1 / 55 (1.82%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Respiratory, thoracic and mediastinal disorders      |                |  |  |
| Bronchopneumopathy                                   |                |  |  |
| subjects affected / exposed                          | 1 / 55 (1.82%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Interstitial lung disease                            |                |  |  |
| subjects affected / exposed                          | 1 / 55 (1.82%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1          |  |  |
| deaths causally related to treatment / all           | 1 / 1          |  |  |
| Lung disorder                                        |                |  |  |
| subjects affected / exposed                          | 2 / 55 (3.64%) |  |  |
| occurrences causally related to treatment / all      | 2 / 2          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Pneumonitis                                          |                |  |  |

|                                                 |                |  |  |
|-------------------------------------------------|----------------|--|--|
| subjects affected / exposed                     | 2 / 55 (3.64%) |  |  |
| occurrences causally related to treatment / all | 2 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Psychiatric disorders                           |                |  |  |
| Anxiety                                         |                |  |  |
| subjects affected / exposed                     | 1 / 55 (1.82%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infections and infestations                     |                |  |  |
| Bronchopulmonary aspergillosis                  |                |  |  |
| subjects affected / exposed                     | 1 / 55 (1.82%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pyelonephritis                                  |                |  |  |
| subjects affected / exposed                     | 1 / 55 (1.82%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

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

| <b>Non-serious adverse events</b>                     | Safety analysis  |  |  |
|-------------------------------------------------------|------------------|--|--|
| Total subjects affected by non-serious adverse events |                  |  |  |
| subjects affected / exposed                           | 50 / 55 (90.91%) |  |  |
| Vascular disorders                                    |                  |  |  |
| Haematoma                                             |                  |  |  |
| subjects affected / exposed                           | 1 / 55 (1.82%)   |  |  |
| occurrences (all)                                     | 1                |  |  |
| Hot flush                                             |                  |  |  |
| subjects affected / exposed                           | 3 / 55 (5.45%)   |  |  |
| occurrences (all)                                     | 3                |  |  |
| Hypertension                                          |                  |  |  |
| subjects affected / exposed                           | 3 / 55 (5.45%)   |  |  |
| occurrences (all)                                     | 3                |  |  |
| Lymphoedema                                           |                  |  |  |

|                                                      |                  |  |  |
|------------------------------------------------------|------------------|--|--|
| subjects affected / exposed                          | 8 / 55 (14.55%)  |  |  |
| occurrences (all)                                    | 8                |  |  |
| General disorders and administration site conditions |                  |  |  |
| Asthenia                                             |                  |  |  |
| subjects affected / exposed                          | 11 / 55 (20.00%) |  |  |
| occurrences (all)                                    | 11               |  |  |
| Chest pain                                           |                  |  |  |
| subjects affected / exposed                          | 1 / 55 (1.82%)   |  |  |
| occurrences (all)                                    | 1                |  |  |
| Face oedema                                          |                  |  |  |
| subjects affected / exposed                          | 1 / 55 (1.82%)   |  |  |
| occurrences (all)                                    | 1                |  |  |
| Fatigue                                              |                  |  |  |
| subjects affected / exposed                          | 27 / 55 (49.09%) |  |  |
| occurrences (all)                                    | 28               |  |  |
| General physical health deterioration                |                  |  |  |
| subjects affected / exposed                          | 1 / 55 (1.82%)   |  |  |
| occurrences (all)                                    | 1                |  |  |
| Hyperthermia                                         |                  |  |  |
| subjects affected / exposed                          | 1 / 55 (1.82%)   |  |  |
| occurrences (all)                                    | 1                |  |  |
| Inflammation                                         |                  |  |  |
| subjects affected / exposed                          | 1 / 55 (1.82%)   |  |  |
| occurrences (all)                                    | 1                |  |  |
| Influenza like illness                               |                  |  |  |
| subjects affected / exposed                          | 1 / 55 (1.82%)   |  |  |
| occurrences (all)                                    | 1                |  |  |
| Malaise                                              |                  |  |  |
| subjects affected / exposed                          | 1 / 55 (1.82%)   |  |  |
| occurrences (all)                                    | 1                |  |  |
| Mucosal inflammation                                 |                  |  |  |
| subjects affected / exposed                          | 28 / 55 (50.91%) |  |  |
| occurrences (all)                                    | 36               |  |  |
| Oedema peripheral                                    |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 6 / 55 (10.91%)  |  |  |
| occurrences (all)                               | 7                |  |  |
| Pain                                            |                  |  |  |
| subjects affected / exposed                     | 3 / 55 (5.45%)   |  |  |
| occurrences (all)                               | 3                |  |  |
| Peripheral swelling                             |                  |  |  |
| subjects affected / exposed                     | 1 / 55 (1.82%)   |  |  |
| occurrences (all)                               | 1                |  |  |
| Pyrexia                                         |                  |  |  |
| subjects affected / exposed                     | 5 / 55 (9.09%)   |  |  |
| occurrences (all)                               | 5                |  |  |
| Drug hypersensitivity                           |                  |  |  |
| subjects affected / exposed                     | 1 / 55 (1.82%)   |  |  |
| occurrences (all)                               | 2                |  |  |
| Reproductive system and breast disorders        |                  |  |  |
| Breast pain                                     |                  |  |  |
| subjects affected / exposed                     | 2 / 55 (3.64%)   |  |  |
| occurrences (all)                               | 2                |  |  |
| Vulvovaginal dryness                            |                  |  |  |
| subjects affected / exposed                     | 1 / 55 (1.82%)   |  |  |
| occurrences (all)                               | 1                |  |  |
| Vulvovaginal inflammation                       |                  |  |  |
| subjects affected / exposed                     | 1 / 55 (1.82%)   |  |  |
| occurrences (all)                               | 1                |  |  |
| Respiratory, thoracic and mediastinal disorders |                  |  |  |
| Asthma                                          |                  |  |  |
| subjects affected / exposed                     | 1 / 55 (1.82%)   |  |  |
| occurrences (all)                               | 1                |  |  |
| Bronchospasm                                    |                  |  |  |
| subjects affected / exposed                     | 1 / 55 (1.82%)   |  |  |
| occurrences (all)                               | 1                |  |  |
| Cough                                           |                  |  |  |
| subjects affected / exposed                     | 12 / 55 (21.82%) |  |  |
| occurrences (all)                               | 13               |  |  |
| Dyspnoea                                        |                  |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 6 / 55 (10.91%) |  |  |
| occurrences (all)           | 8               |  |  |
| Dysphonia                   |                 |  |  |
| subjects affected / exposed | 2 / 55 (3.64%)  |  |  |
| occurrences (all)           | 2               |  |  |
| Dyspnoea exertional         |                 |  |  |
| subjects affected / exposed | 2 / 55 (3.64%)  |  |  |
| occurrences (all)           | 21              |  |  |
| Epistaxis                   |                 |  |  |
| subjects affected / exposed | 6 / 55 (10.91%) |  |  |
| occurrences (all)           | 6               |  |  |
| Interstitial lung disease   |                 |  |  |
| subjects affected / exposed | 1 / 55 (1.82%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Lung disorder               |                 |  |  |
| subjects affected / exposed | 2 / 55 (3.64%)  |  |  |
| occurrences (all)           | 2               |  |  |
| Nasal dryness               |                 |  |  |
| subjects affected / exposed | 1 / 55 (1.82%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Nasal ulcer                 |                 |  |  |
| subjects affected / exposed | 1 / 55 (1.82%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Oropharyngeal pain          |                 |  |  |
| subjects affected / exposed | 2 / 55 (3.64%)  |  |  |
| occurrences (all)           | 2               |  |  |
| Pleural effusion            |                 |  |  |
| subjects affected / exposed | 1 / 55 (1.82%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Pneumonitis                 |                 |  |  |
| subjects affected / exposed | 2 / 55 (3.64%)  |  |  |
| occurrences (all)           | 2               |  |  |
| Productive cough            |                 |  |  |
| subjects affected / exposed | 1 / 55 (1.82%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Psychiatric disorders       |                 |  |  |



|                                                                                                            |                      |  |  |
|------------------------------------------------------------------------------------------------------------|----------------------|--|--|
| Anxiety<br>subjects affected / exposed<br>occurrences (all)                                                | 2 / 55 (3.64%)<br>2  |  |  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                                               | 5 / 55 (9.09%)<br>5  |  |  |
| Sleep disorder<br>subjects affected / exposed<br>occurrences (all)                                         | 1 / 55 (1.82%)<br>1  |  |  |
| Investigations<br>Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)   | 3 / 55 (5.45%)<br>3  |  |  |
| Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)                   | 3 / 55 (5.45%)<br>3  |  |  |
| Transaminases increased<br>subjects affected / exposed<br>occurrences (all)                                | 5 / 55 (9.09%)<br>6  |  |  |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                                       | 6 / 55 (10.91%)<br>6 |  |  |
| Weight increased<br>subjects affected / exposed<br>occurrences (all)                                       | 1 / 55 (1.82%)<br>1  |  |  |
| Injury, poisoning and procedural complications<br>Fall<br>subjects affected / exposed<br>occurrences (all) | 1 / 55 (1.82%)<br>1  |  |  |
| Limb injury<br>subjects affected / exposed<br>occurrences (all)                                            | 1 / 55 (1.82%)<br>1  |  |  |
| Nervous system disorders<br>Ageusia<br>subjects affected / exposed<br>occurrences (all)                    | 2 / 55 (3.64%)<br>2  |  |  |

|                                      |                  |  |  |
|--------------------------------------|------------------|--|--|
| Carpal tunnel syndrome               |                  |  |  |
| subjects affected / exposed          | 1 / 55 (1.82%)   |  |  |
| occurrences (all)                    | 1                |  |  |
| Dizziness                            |                  |  |  |
| subjects affected / exposed          | 1 / 55 (1.82%)   |  |  |
| occurrences (all)                    | 1                |  |  |
| Dysgeusia                            |                  |  |  |
| subjects affected / exposed          | 3 / 55 (5.45%)   |  |  |
| occurrences (all)                    | 4                |  |  |
| Headache                             |                  |  |  |
| subjects affected / exposed          | 10 / 55 (18.18%) |  |  |
| occurrences (all)                    | 10               |  |  |
| Paraesthesia                         |                  |  |  |
| subjects affected / exposed          | 1 / 55 (1.82%)   |  |  |
| occurrences (all)                    | 1                |  |  |
| Peripheral sensory neuropathy        |                  |  |  |
| subjects affected / exposed          | 1 / 55 (1.82%)   |  |  |
| occurrences (all)                    | 1                |  |  |
| Taste disorder                       |                  |  |  |
| subjects affected / exposed          | 1 / 55 (1.82%)   |  |  |
| occurrences (all)                    | 1                |  |  |
| Blood and lymphatic system disorders |                  |  |  |
| Anaemia                              |                  |  |  |
| subjects affected / exposed          | 13 / 55 (23.64%) |  |  |
| occurrences (all)                    | 14               |  |  |
| Hyperleukocytosis                    |                  |  |  |
| subjects affected / exposed          | 1 / 55 (1.82%)   |  |  |
| occurrences (all)                    | 1                |  |  |
| Neutropenia                          |                  |  |  |
| subjects affected / exposed          | 1 / 55 (1.82%)   |  |  |
| occurrences (all)                    | 1                |  |  |
| Thrombocytopenia                     |                  |  |  |
| subjects affected / exposed          | 4 / 55 (7.27%)   |  |  |
| occurrences (all)                    | 4                |  |  |
| Ear and labyrinth disorders          |                  |  |  |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                       |  |  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|
| Vertigo<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 1 / 55 (1.82%)<br>1                                                                                                                                                                                                   |  |  |
| Eye disorders<br>Dry eye<br>subjects affected / exposed<br>occurrences (all)<br><br>Ocular hyperaemia<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 1 / 55 (1.82%)<br>1<br><br>1 / 55 (1.82%)<br>1                                                                                                                                                                        |  |  |
| Gastrointestinal disorders<br>Abdominal pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)<br><br>Anal fissure<br>subjects affected / exposed<br>occurrences (all)<br><br>Anorectal discomfort<br>subjects affected / exposed<br>occurrences (all)<br><br>Constipation<br>subjects affected / exposed<br>occurrences (all)<br><br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Dry mouth<br>subjects affected / exposed<br>occurrences (all)<br><br>Dyspepsia<br>subjects affected / exposed<br>occurrences (all)<br><br>Dysphagia | 1 / 55 (1.82%)<br>1<br><br>6 / 55 (10.91%)<br>6<br><br>2 / 55 (3.64%)<br>2<br><br>1 / 55 (1.82%)<br>1<br><br>7 / 55 (12.73%)<br>7<br><br>14 / 55 (25.45%)<br>15<br><br>1 / 55 (1.82%)<br>1<br><br>2 / 55 (3.64%)<br>2 |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 55 (1.82%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Gastritis                   |                 |  |  |
| subjects affected / exposed | 1 / 55 (1.82%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Gastroenteritis             |                 |  |  |
| subjects affected / exposed | 1 / 55 (1.82%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Gastrointestinal disorder   |                 |  |  |
| subjects affected / exposed | 2 / 55 (3.64%)  |  |  |
| occurrences (all)           | 2               |  |  |
| Haemorrhoids                |                 |  |  |
| subjects affected / exposed | 3 / 55 (5.45%)  |  |  |
| occurrences (all)           | 3               |  |  |
| Nausea                      |                 |  |  |
| subjects affected / exposed | 7 / 55 (12.73%) |  |  |
| occurrences (all)           | 8               |  |  |
| Oesophagitis                |                 |  |  |
| subjects affected / exposed | 2 / 55 (3.64%)  |  |  |
| occurrences (all)           | 2               |  |  |
| Proctalgia                  |                 |  |  |
| subjects affected / exposed | 1 / 55 (1.82%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Rectal haemorrhage          |                 |  |  |
| subjects affected / exposed | 2 / 55 (3.64%)  |  |  |
| occurrences (all)           | 2               |  |  |
| Stomatitis                  |                 |  |  |
| subjects affected / exposed | 8 / 55 (14.55%) |  |  |
| occurrences (all)           | 9               |  |  |
| Toothache                   |                 |  |  |
| subjects affected / exposed | 1 / 55 (1.82%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Vomiting                    |                 |  |  |
| subjects affected / exposed | 3 / 55 (5.45%)  |  |  |
| occurrences (all)           | 4               |  |  |
| Chest pain                  |                 |  |  |

|                                            |                 |  |  |
|--------------------------------------------|-----------------|--|--|
| subjects affected / exposed                | 1 / 55 (1.82%)  |  |  |
| occurrences (all)                          | 1               |  |  |
| Skin and subcutaneous tissue disorders     |                 |  |  |
| Acne                                       |                 |  |  |
| subjects affected / exposed                | 2 / 55 (3.64%)  |  |  |
| occurrences (all)                          | 2               |  |  |
| Alopecia                                   |                 |  |  |
| subjects affected / exposed                | 2 / 55 (3.64%)  |  |  |
| occurrences (all)                          | 2               |  |  |
| Dry skin                                   |                 |  |  |
| subjects affected / exposed                | 8 / 55 (14.55%) |  |  |
| occurrences (all)                          | 8               |  |  |
| Eczema                                     |                 |  |  |
| subjects affected / exposed                | 2 / 55 (3.64%)  |  |  |
| occurrences (all)                          | 2               |  |  |
| Erythema                                   |                 |  |  |
| subjects affected / exposed                | 2 / 55 (3.64%)  |  |  |
| occurrences (all)                          | 2               |  |  |
| Hyperhidrosis                              |                 |  |  |
| subjects affected / exposed                | 1 / 55 (1.82%)  |  |  |
| occurrences (all)                          | 1               |  |  |
| Nail toxicity                              |                 |  |  |
| subjects affected / exposed                | 1 / 55 (1.82%)  |  |  |
| occurrences (all)                          | 1               |  |  |
| Onychalgia                                 |                 |  |  |
| subjects affected / exposed                | 1 / 55 (1.82%)  |  |  |
| occurrences (all)                          | 1               |  |  |
| Onychoclasia                               |                 |  |  |
| subjects affected / exposed                | 1 / 55 (1.82%)  |  |  |
| occurrences (all)                          | 1               |  |  |
| Palmar-plantar erythrodysesthesia syndrome |                 |  |  |
| subjects affected / exposed                | 1 / 55 (1.82%)  |  |  |
| occurrences (all)                          | 1               |  |  |
| Photosensitivity reaction                  |                 |  |  |

|                             |                  |  |  |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 1 / 55 (1.82%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Pruritus                    |                  |  |  |
| subjects affected / exposed | 8 / 55 (14.55%)  |  |  |
| occurrences (all)           | 8                |  |  |
| Rash                        |                  |  |  |
| subjects affected / exposed | 17 / 55 (30.91%) |  |  |
| occurrences (all)           | 21               |  |  |
| Rash maculo-papular         |                  |  |  |
| subjects affected / exposed | 2 / 55 (3.64%)   |  |  |
| occurrences (all)           | 2                |  |  |
| Skin fissures               |                  |  |  |
| subjects affected / exposed | 1 / 55 (1.82%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Skin lesion                 |                  |  |  |
| subjects affected / exposed | 1 / 55 (1.82%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Skin ulcer                  |                  |  |  |
| subjects affected / exposed | 1 / 55 (1.82%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Renal and urinary disorders |                  |  |  |
| Acute kidney injury         |                  |  |  |
| subjects affected / exposed | 1 / 55 (1.82%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Pollakiuria                 |                  |  |  |
| subjects affected / exposed | 1 / 55 (1.82%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Renal pain                  |                  |  |  |
| subjects affected / exposed | 1 / 55 (1.82%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Endocrine disorders         |                  |  |  |
| Diabetes insipidus          |                  |  |  |
| subjects affected / exposed | 1 / 55 (1.82%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Hypothyroidism              |                  |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 1 / 55 (1.82%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Musculoskeletal and connective tissue disorders |                 |  |  |
| Arthralgia                                      |                 |  |  |
| subjects affected / exposed                     | 7 / 55 (12.73%) |  |  |
| occurrences (all)                               | 7               |  |  |
| Back pain                                       |                 |  |  |
| subjects affected / exposed                     | 5 / 55 (9.09%)  |  |  |
| occurrences (all)                               | 5               |  |  |
| Bone pain                                       |                 |  |  |
| subjects affected / exposed                     | 9 / 55 (16.36%) |  |  |
| occurrences (all)                               | 10              |  |  |
| Myalgia                                         |                 |  |  |
| subjects affected / exposed                     | 3 / 55 (5.45%)  |  |  |
| occurrences (all)                               | 3               |  |  |
| Osteonecrosis of jaw                            |                 |  |  |
| subjects affected / exposed                     | 1 / 55 (1.82%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Pain in extremity                               |                 |  |  |
| subjects affected / exposed                     | 4 / 55 (7.27%)  |  |  |
| occurrences (all)                               | 4               |  |  |
| Pain in jaw                                     |                 |  |  |
| subjects affected / exposed                     | 1 / 55 (1.82%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Infections and infestations                     |                 |  |  |
| Bartholin's abscess                             |                 |  |  |
| subjects affected / exposed                     | 1 / 55 (1.82%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Conjunctivitis                                  |                 |  |  |
| subjects affected / exposed                     | 3 / 55 (5.45%)  |  |  |
| occurrences (all)                               | 3               |  |  |
| Cystitis                                        |                 |  |  |
| subjects affected / exposed                     | 2 / 55 (3.64%)  |  |  |
| occurrences (all)                               | 3               |  |  |
| Erysipelas                                      |                 |  |  |

|                             |                |  |  |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 1 / 55 (1.82%) |  |  |
| occurrences (all)           | 1              |  |  |
| Folliculitis                |                |  |  |
| subjects affected / exposed | 3 / 55 (5.45%) |  |  |
| occurrences (all)           | 3              |  |  |
| Genital herpes simplex      |                |  |  |
| subjects affected / exposed | 1 / 55 (1.82%) |  |  |
| occurrences (all)           | 1              |  |  |
| Gingivitis                  |                |  |  |
| subjects affected / exposed | 1 / 55 (1.82%) |  |  |
| occurrences (all)           | 2              |  |  |
| Localised infection         |                |  |  |
| subjects affected / exposed | 1 / 55 (1.82%) |  |  |
| occurrences (all)           | 1              |  |  |
| Infection                   |                |  |  |
| subjects affected / exposed | 1 / 55 (1.82%) |  |  |
| occurrences (all)           | 1              |  |  |
| Mastitis                    |                |  |  |
| subjects affected / exposed | 1 / 55 (1.82%) |  |  |
| occurrences (all)           | 1              |  |  |
| Nasopharyngitis             |                |  |  |
| subjects affected / exposed | 2 / 55 (3.64%) |  |  |
| occurrences (all)           | 2              |  |  |
| Pharyngitis                 |                |  |  |
| subjects affected / exposed | 1 / 55 (1.82%) |  |  |
| occurrences (all)           | 1              |  |  |
| Pneumonia                   |                |  |  |
| subjects affected / exposed | 2 / 55 (3.64%) |  |  |
| occurrences (all)           | 2              |  |  |
| Pneumonia haemophilus       |                |  |  |
| subjects affected / exposed | 1 / 55 (1.82%) |  |  |
| occurrences (all)           | 1              |  |  |
| Respiratory tract infection |                |  |  |
| subjects affected / exposed | 1 / 55 (1.82%) |  |  |
| occurrences (all)           | 1              |  |  |
| Rhinitis                    |                |  |  |



|                                    |                  |  |  |
|------------------------------------|------------------|--|--|
| subjects affected / exposed        | 5 / 55 (9.09%)   |  |  |
| occurrences (all)                  | 5                |  |  |
| Sinusitis                          |                  |  |  |
| subjects affected / exposed        | 3 / 55 (5.45%)   |  |  |
| occurrences (all)                  | 3                |  |  |
| Tracheitis                         |                  |  |  |
| subjects affected / exposed        | 1 / 55 (1.82%)   |  |  |
| occurrences (all)                  | 1                |  |  |
| Urinary tract infection            |                  |  |  |
| subjects affected / exposed        | 5 / 55 (9.09%)   |  |  |
| occurrences (all)                  | 5                |  |  |
| Wound infection                    |                  |  |  |
| subjects affected / exposed        | 1 / 55 (1.82%)   |  |  |
| occurrences (all)                  | 1                |  |  |
| Skin injury                        |                  |  |  |
| subjects affected / exposed        | 1 / 55 (1.82%)   |  |  |
| occurrences (all)                  | 1                |  |  |
| Blood creatinine increased         |                  |  |  |
| subjects affected / exposed        | 2 / 55 (3.64%)   |  |  |
| occurrences (all)                  | 2                |  |  |
| Metabolism and nutrition disorders |                  |  |  |
| Decreased appetite                 |                  |  |  |
| subjects affected / exposed        | 19 / 55 (34.55%) |  |  |
| occurrences (all)                  | 20               |  |  |
| Diabetes mellitus                  |                  |  |  |
| subjects affected / exposed        | 1 / 55 (1.82%)   |  |  |
| occurrences (all)                  | 1                |  |  |
| Dyslipidaemia                      |                  |  |  |
| subjects affected / exposed        | 3 / 55 (5.45%)   |  |  |
| occurrences (all)                  | 3                |  |  |
| Hypercholesterolaemia              |                  |  |  |
| subjects affected / exposed        | 4 / 55 (7.27%)   |  |  |
| occurrences (all)                  | 4                |  |  |
| Hyperglycaemia                     |                  |  |  |
| subjects affected / exposed        | 7 / 55 (12.73%)  |  |  |
| occurrences (all)                  | 7                |  |  |

|                              |                |  |  |
|------------------------------|----------------|--|--|
| Hypertriglyceridaemia        |                |  |  |
| subjects affected / exposed  | 1 / 55 (1.82%) |  |  |
| occurrences (all)            | 2              |  |  |
| Hypocalcaemia                |                |  |  |
| subjects affected / exposed  | 2 / 55 (3.64%) |  |  |
| occurrences (all)            | 2              |  |  |
| Hypokalaemia                 |                |  |  |
| subjects affected / exposed  | 3 / 55 (5.45%) |  |  |
| occurrences (all)            | 3              |  |  |
| Hypomagnesaemia              |                |  |  |
| subjects affected / exposed  | 1 / 55 (1.82%) |  |  |
| occurrences (all)            | 1              |  |  |
| Hyponatraemia                |                |  |  |
| subjects affected / exposed  | 1 / 55 (1.82%) |  |  |
| occurrences (all)            | 1              |  |  |
| Vitamin B complex deficiency |                |  |  |
| subjects affected / exposed  | 1 / 55 (1.82%) |  |  |
| occurrences (all)            | 1              |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                                                         |
|------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 23 May 2014      | Protocol v2.0 :<br>-Clarification of haematology baseline assessments<br>-Clarification of PET timelines<br>-Change of efficacy assessment time point from every 8 weeks to 12 weeks to be in accordance with the reimbursement conditions for Afinitor in combination with exemestane.                           |
| 15 May 2017      | Protocol v3.0<br>- Add Pilot phase results (Second FDG PET/CT timepoint selected for the main phase)<br>- Main phase sample size's recalculation<br>- Modification of schedule of assessment<br>- Modification of samples collection and translational researches<br>- Clarification inclusion/exclusion criteria |
| 20 June 2017     | Protocol v4.0 : Modification of inclusion criteria                                                                                                                                                                                                                                                                |
| 07 December 2020 | Protocol v5.0<br>- Modification of the end of study definition<br>- Modification of the secondary objective<br>- Addition of a sample<br>- Clarification regarding TR analyses                                                                                                                                    |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date         | Interruption                                          | Restart date |
|--------------|-------------------------------------------------------|--------------|
| 30 June 2016 | Last subject included in the pilot phase of the study | 22 May 2017  |

Notes:

### Limitations and caveats

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

There were no limitations and caveats applicable to this summary of the results.

Notes:

### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/34548493>

<http://www.ncbi.nlm.nih.gov/pubmed/35296682>