



## Clinical trial results:

### The LuMEEn study

### 177Lu-octreotate treatment outcome prediction using Multimodality imaging in refractory neuroEndocrine tumours

#### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2012-003666-41    |
| Trial protocol           | BE                |
| Global end of trial date | 16 September 2022 |

#### Results information

|                                   |  |
|-----------------------------------|--|
| Result version number             | v1 (current)   |
| This version publication date     | 13 October 2024                                      |
| First version publication date    | 13 October 2024                                      |
| Summary attachment (see zip file) | Final Study Report (2012-003666-41-final-report.pdf) |

#### Trial information

##### Trial identification

|                       |            |
|-----------------------|------------|
| Sponsor protocol code | IJBMNLUMEN |
|-----------------------|------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01842165 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Institut Jules Bordet  |
| Sponsor organisation address | rue Meylemeersch 90, Anderlecht, Belgium, 1200                                 |
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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                       | 24 August 2023    |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 20 May 2022       |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 16 September 2022 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

For each lesion: To assess the value of the following parameters (obtained through functional and molecular imaging) for predicting the lesion-by-lesion PRRT treatment outcome:

- 18FDG uptake on 18FDG PET/CT,
  - 68Ga-octreotate uptake on 68Ga-octreotate PET/CT,
  - Apparent Diffusion Coefficient on Diffusion Weighted-MRI,
- [for these three parameters, absolute values at baseline will be assessed]
- Tumor dosimetry on post-177Lu-octreotate SPECT/CT after the first cycle.

Protection of trial subjects:

a nephroprotective perfusion of an amino acid solution was simultaneously administered with the 177Lu-octreotate injection. This nephroprotective perfusion was preceded by the administration of an anti-emetic regiment to prevent nausea or vomiting from the amino acids.

Background therapy: -

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 25 July 2013 |
| 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: 37 |
| Worldwide total number of subjects   | 37          |
| EEA total number of subjects         | 37          |

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) | 13 |
| From 65 to 84 years  | 24 |
| 85 years and over    | 0  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Screening procedures were done within 4 weeks before the first <sup>177</sup>Lu-octreotate injection.

### Period 1

|                              |                            |
|------------------------------|----------------------------|
| Period 1 title               | Treatment (overall period) |
| Is this the baseline period? | Yes                        |
| Allocation method            | Not applicable             |
| Blinding used                | Not blinded                |

### Arms

|                  |                 |
|------------------|-----------------|
| <b>Arm title</b> | 77Lu-octreotate |
|------------------|-----------------|

Arm description:

This treatment consisted of <sup>177</sup>Lu-octreotate injections(4 cycles) in fixed activities of 7,4GBq (200 mCi) ( $\pm 5\%$ ) each, given 12 weeks ( $\pm 1$ week) apart, injected intravenously, simultaneously with nephroprotective perfusion of an amino acid solution.

|  |   |
|--|---|
| Arm type                               | Experimental                            |
| Investigational medicinal product name | Lu-octreotate                           |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Radiopharmaceutical precursor, solution |
| Routes of administration               | Injection                               |

Dosage and administration details:

(4 cycles) in fixed activities of 7,4GBq (200 mCi) ( $\pm 5\%$ ) each, given 12 weeks ( $\pm 1$ week) apart, injected intravenously, simultaneously with nephroprotective perfusion of an amino acid solution

| Number of subjects in period 1 | 77Lu-octreotate |
|--------------------------------|-----------------|
| Started                        | 37              |
| Completed                      | 28              |
| Not completed                  | 9               |
| Consent withdrawn by subject   | 3               |
| Second primary malignancy      | 2               |
| Disease progression            | 2               |
| Death                          | 1               |
| Lost to follow-up              | 1               |

## Baseline characteristics

### Reporting groups

| Reporting group title          | Treatment |
|--------------------------------|-----------|
| Reporting group description: - |           |

| Reporting group values                                | Treatment | Total |  |
|---|-----------|-------|--|
| Number of subjects                                    | 37        | 37    |  |
| Age categorical                                       |           |       |  |
| 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<br>months)           | 0         | 0     |  |
| Children (2-11 years)                                 | 0         | 0     |  |
| Adolescents (12-17 years)                             | 0         | 0     |  |
| Adults (18-64 years)                                  | 13        | 13    |  |
| From 65-84 years                                      | 24        | 24    |  |
| 85 years and over                                     | 0         | 0     |  |
| Age continuous  |           |       |  |
| Units: years  |           |       |  |
| arithmetic mean                                       | 66        |       |  |
| standard deviation                                    | ± 8.1     | -     |  |
| Gender categorical                                    |           |       |  |
| Units: Subjects                                       |           |       |  |
| Female  | 18        | 18    |  |
| Male  | 19        | 19    |  |
| tumour grade  |           |       |  |
| Units: Subjects                                       |           |       |  |
| grade 1   | 12        | 12    |  |
| grade 2   | 22        | 22    |  |
| grade 3   | 3         | 3     |  |
| primary tumour site                                   |           |       |  |
| Units: Subjects                                       |           |       |  |
| small intestinal                                      | 23        | 23    |  |
| pancreatic  | 10        | 10    |  |
| colorectal  | 4         | 4     |  |
| site of metastasis: liver                             |           |       |  |
| Units: Subjects                                       |           |       |  |
| Yes   | 32        | 32    |  |
| No  | 5         | 5     |  |
| site of metastases: lymph nodes                       |           |       |  |
| Units: Subjects                                       |           |       |  |
| Yes   | 31        | 31    |  |
| No  | 6         | 6     |  |
| site of metastasis: bone                              |           |       |  |
| Units: Subjects                                       |           |       |  |

|   |    |    |  |
|---|----|----|--|
| Yes   | 22 | 22 |  |
| No  | 15 | 15 |  |
| site of metastases: peritoneum<br>Units: Subjects   |    |    |  |
| Yes   | 12 | 12 |  |
| No  | 25 | 25 |  |
| site of metastases : pancreas<br>Units: Subjects  |    |    |  |
| Yes   | 3  | 3  |  |
| No  | 34 | 34 |  |
| site of metastasis: lung<br>Units: Subjects   |    |    |  |
| Yes   | 2  | 2  |  |
| No  | 35 | 35 |  |
| site of metastases: other (pleural,<br>adrenal, ovary, mesentery/pelvic)<br>Units: Subjects |    |    |  |
| Yes   | 6  | 6  |  |
| No  | 31 | 31 |  |
| symptoms: diarrhoea<br>Units: Subjects  |    |    |  |
| Yes   | 16 | 16 |  |
| No  | 21 | 21 |  |
| symptoms: pain<br>Units: Subjects   |    |    |  |
| Yes   | 15 | 15 |  |
| No  | 22 | 22 |  |
| symptoms: fatigue<br>Units: Subjects  |    |    |  |
| Yes   | 11 | 11 |  |
| No  | 26 | 26 |  |
| symptoms: flushes<br>Units: Subjects  |    |    |  |
| Yes   | 9  | 9  |  |
| No  | 28 | 28 |  |
| No symptoms<br>Units: Subjects  |    |    |  |
| Yes   | 12 | 12 |  |
| no  | 25 | 25 |  |
| Positive 18FDG-PET/CT<br>Units: Subjects  |    |    |  |
| Yes   | 15 | 15 |  |
| No  | 22 | 22 |  |
| surgery (including primary tumour<br>resection)<br>Units: Subjects                          |    |    |  |
| Yes   | 27 | 27 |  |
| No  | 10 | 10 |  |
| SSAs<br>Units: Subjects   |    |    |  |
| Yes   | 36 | 36 |  |
| No  | 1  | 1  |  |

|  |    |    |  |
|--|----|----|--|
| targeted therapy (including everolimus and sunitinib)<br>Units: Subjects   |    |    |  |
| Yes  | 11 | 11 |  |
| No   | 26 | 26 |  |
| liver targeted therapy (including chemo-embolisation, radio-embolisation and radiofrequency ablation)<br>Units: Subjects |    |    |  |
| Yes  | 8  | 8  |  |
| No   | 29 | 29 |  |
| radiotherapy (external beam radiation)<br>Units: Subjects  |    |    |  |
| Yes  | 4  | 4  |  |
| No   | 33 | 33 |  |
| interferon<br>Units: Subjects  |    |    |  |
| Yes  | 1  | 1  |  |
| No   | 36 | 36 |  |

## End points

### End points reporting groups

|   |                 |
|---|-----------------|
| Reporting group title   | 77Lu-octreotate |
| Reporting group description:<br>This treatment consisted of 177Lu-octreotate injections(4 cycles) in fixed activities of 7,4GBq (200 mCi) ( $\pm 5\%$ ) each, given 12 weeks ( $\pm 1$ week) apart, injected intravenously, simultaneously with nephroprotective perfusion of an amino acid solution. |                 |

### Primary: Lesion time to progression (TTP) (lesion-based analysis)

|   |   |
|---|---|
| End point title   | Lesion time to progression (TTP) (lesion-based analysis) <sup>[1]</sup> |
| End point description:<br>116 target lesions. 84 out of 116 were considered evaluable.<br>1) 18FDG PET/CT imaging: No significant association with the lesion morphological outcome was observed for any of the 18FDG PET baseline parameters.<br>2) 68Ga-DOTATATE PET/CT imaging: Baseline SUVmax, SUVmean, tumour-to-blood ratio, SSTR-TV and total lesion SSTR expression were not associated with the lesion morphological outcome.<br>3) dwMR imaging: In 62 morphologically evaluable lesions, no association was found between baseline ADC and lesion outcome ( $p=0.58$ ). |   |

|   |         |
|---|---------|
| End point type  | Primary |
| End point timeframe:<br>Median follow-up time for all subjects (data analysis in July 2022) was 57 months (95%CI: 50-71), during which the median lesion-based TTP was not reached. |         |

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: This is a single arm study.

| End point values                | 77Lu-octreotate   |  |  |  |
|---------------------------------|-------------------|--|--|--|
| Subject group type              | Reporting group   |  |  |  |
| Number of subjects analysed     | 37 <sup>[2]</sup> |  |  |  |
| Units: evaluable target lesions |                   |  |  |  |
| complete response               | 0                 |  |  |  |
| partial response                | 22                |  |  |  |
| stable                          | 50                |  |  |  |
| progression                     | 12                |  |  |  |

Notes:

[2] - 84 evaluable target lesions

### Statistical analyses

No statistical analyses for this end point

### Secondary: objective response (patient-based analysis)

|  |   |
|--|---|
| End point title  | objective response (patient-based analysis) |
| End point description:   |   |
| End point type   | Secondary                                   |
| End point timeframe:<br>The median follow-up time (data cutoff, July 2022) was 57 months (95% CI, 50-71 months). |   |



| End point values            | 77Lu-octreotate   |  |  |  |
|-----------------------------|-------------------|--|--|--|
| Subject group type          | Reporting group   |  |  |  |
| Number of subjects analysed | 37 <sup>[3]</sup> |  |  |  |
| Units: number of patients   |                   |  |  |  |
| complete response           | 0                 |  |  |  |
| partial response            | 11                |  |  |  |
| stable disease              | 24                |  |  |  |
| progression                 | 2                 |  |  |  |

Notes:

[3] - 37 treated patients

### Statistical analyses

No statistical analyses for this end point

### Secondary: Progression-free survival

|   |                           |
|---|---------------------------|
| End point title   | Progression-free survival |
| End point description:  |                           |
| <p>Patients with pancreatic primary NETs had a shorter PFS (median, 19.4 months) than that of patients with intestinal NETs (29.5 months) (P-value=0.01; HR,2.96; 95% CI, 1.25–7.02). 1) 68Ga-DOTATATE PET/CT: An SSTR TV decrease of more than 10% from baseline after C1 discriminated patients with a significantly longer median PFS (51.3 months) than that (22.8 months) of patients for whom SSTR TV increased or decreased by less than 10% (P-value=0.003; HR, 0.35; 95% CI, 0.16–0.75). 2) 18F-FDG PET/CT. Quantification of baseline 18F-FDG PET/CT was available for only 10 patients. Because of the low number of patients and events, no statistical analysis for association with patient outcome was performed. 3) Diffusion-Weighted MRI: In 29 patients followed by MRI, there was no statistical evidence of an association between baseline ADC or its relative change after C1 and patient outcome.</p> |                           |
| End point type  | Secondary                 |
| End point timeframe:  |                           |
| Median follow-up: 57 months   |                           |

| End point values                      | 77Lu-octreotate     |  |  |  |
|---------------------------------------|---------------------|--|--|--|
| Subject group type                    | Reporting group     |  |  |  |
| Number of subjects analysed           | 37 <sup>[4]</sup>   |  |  |  |
| Units: months                         |                     |  |  |  |
| median (inter-quartile range (Q1-Q3)) | 28.1 (21.7 to 48.1) |  |  |  |

Notes:

[4] - treated patients

### Statistical analyses

No statistical analyses for this end point

### Secondary: tumor dosimetry

|   |                 |
|---|-----------------|
| End point title   | tumor dosimetry |
| End point description:  |                 |
| 83 target lesions: The median absorbed dose in C1 was 33Gy (IQR, 22–50 Gy) and declined from the first to the last treatment cycles, reaching significance between C1 and cycle 3 (P-value=0.002), C1 and cycle 4 (P-value<0.001), and cycles 2 and 4 (P-value=0.01). A significant correlation between tumor-absorbed C1 dose and lesion outcome was demonstrated for larger lesions ( $\geq 22\text{mm}$ ) and for the limited number of lesions of colorectal primary NET origin. On a patient level, the minimal absorbed dose per target lesion in C1 ranged from 10 to 77Gy. An optimal cutoff of 35Gy (i.e., patients in whom all target lesions received at least a 35-Gy tumor-absorbed C1 dose) discriminated patients with a significantly longer median PFS (48.1 months) than that of patients in whom at least 1 target lesion was treated with less than 35Gy in C1 (26.2 months) (P-value=0.02; HR, 0.37; 95% CI, 0.17–0.82). |                 |
| End point type  | Secondary       |
| End point timeframe:  |                 |
| absorbed dose in C1 (cycle 1)   |                 |

|                                       |                   |  |  |  |
|---------------------------------------|-------------------|--|--|--|
| <b>End point values</b>               | 77Lu-octreotate   |  |  |  |
| Subject group type                    | Reporting group   |  |  |  |
| Number of subjects analysed           | 37 <sup>[5]</sup> |  |  |  |
| Units: Gy                             |                   |  |  |  |
| median (inter-quartile range (Q1-Q3)) | 33 (22 to 50)     |  |  |  |

Notes:

[5] - treated patients

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Glomerular filtration rate (GFR) decrease between start and end of treatment

|  |  |
|--|--|
| End point title                                  | Glomerular filtration rate (GFR) decrease between start and end of treatment |
| End point description:                           |  |
| End point type                                   | Other pre-specified  |
| End point timeframe:                             |  |
| end of treatment, median follow-up of 23 months. |  |

|                                       |                   |  |  |  |
|---------------------------------------|-------------------|--|--|--|
| <b>End point values</b>               | 77Lu-octreotate   |  |  |  |
| Subject group type                    | Reporting group   |  |  |  |
| Number of subjects analysed           | 37 <sup>[6]</sup> |  |  |  |
| Units: relative decrease (%)          |                   |  |  |  |
| median (inter-quartile range (Q1-Q3)) | -11 (-17 to 3)    |  |  |  |

Notes:

[6] - treated patients

## Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

from the first administration of 177Lu-octreotate until 12 weeks after the last dose of 177Lu-octreotate

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

### Dictionary used

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

|                    |    |
|--------------------|----|
| Dictionary version | 26 |
|--------------------|----|

### Reporting groups

|                       |                              |
|-----------------------|------------------------------|
| Reporting group title | Exposed to 177Lu-octreotate: |
|-----------------------|------------------------------|

Reporting group description: -

| Serious adverse events  | Exposed to 177Lu-octreotate: |  |  |
|---|------------------------------|--|--|
| Total subjects affected by serious adverse events                   |                              |  |  |
| subjects affected / exposed   | 13 / 37 (35.14%)             |  |  |
| number of deaths (all causes)                                       | 0                            |  |  |
| number of deaths resulting from adverse events                      | 0                            |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                              |  |  |
| Myelodysplastic syndrome  |                              |  |  |
| subjects affected / exposed   | 2 / 37 (5.41%)               |  |  |
| occurrences causally related to treatment / all                     | 1 / 2                        |  |  |
| deaths causally related to treatment / all                          | 0 / 0                        |  |  |
| Injury, poisoning and procedural complications                      |                              |  |  |
| Incisional hernia   |                              |  |  |
| subjects affected / exposed   | 1 / 37 (2.70%)               |  |  |
| occurrences causally related to treatment / all                     | 0 / 1                        |  |  |
| deaths causally related to treatment / all                          | 0 / 0                        |  |  |
| Spinal compression fracture   |                              |  |  |
| subjects affected / exposed   | 1 / 37 (2.70%)               |  |  |
| occurrences causally related to treatment / all                     | 0 / 1                        |  |  |
| deaths causally related to treatment / all                          | 0 / 0                        |  |  |
| Cardiac disorders   |                              |  |  |
| Cardiac failure   |                              |  |  |

|  |                |  |  |
|--|----------------|--|--|
| subjects affected / exposed                          | 1 / 37 (2.70%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Blood and lymphatic system disorders                 |                |  |  |
| Anaemia  |                |  |  |
| subjects affected / exposed                          | 1 / 37 (2.70%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| General disorders and administration site conditions |                |  |  |
| Inflammation   |                |  |  |
| subjects affected / exposed                          | 1 / 37 (2.70%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Pyrexia  |                |  |  |
| subjects affected / exposed                          | 1 / 37 (2.70%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Immune system disorders                              |                |  |  |
| Anaphylactic reaction                                |                |  |  |
| subjects affected / exposed                          | 1 / 37 (2.70%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 1          |  |  |
| Gastrointestinal disorders                           |                |  |  |
| Abdominal pain upper                                 |                |  |  |
| subjects affected / exposed                          | 1 / 37 (2.70%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Ascites  |                |  |  |
| subjects affected / exposed                          | 2 / 37 (5.41%) |  |  |
| occurrences causally related to treatment / all      | 1 / 2          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Intestinal ischaemia                                 |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 37 (2.70%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pancreatitis acute                              |                |  |  |
| subjects affected / exposed                     | 1 / 37 (2.70%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Small intestinal obstruction                    |                |  |  |
| subjects affected / exposed                     | 1 / 37 (2.70%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Subileus  |                |  |  |
| subjects affected / exposed                     | 2 / 37 (5.41%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hepatobiliary disorders                         |                |  |  |
| Cholecystitis acute                             |                |  |  |
| subjects affected / exposed                     | 1 / 37 (2.70%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Renal and urinary disorders                     |                |  |  |
| Hydronephrosis                                  |                |  |  |
| subjects affected / exposed                     | 1 / 37 (2.70%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infections and infestations                     |                |  |  |
| Bacteroides infection                           |                |  |  |
| subjects affected / exposed                     | 1 / 37 (2.70%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

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

|   |                              |  |  |
|---|------------------------------|--|--|
| <b>Non-serious adverse events</b>                                   | Exposed to 177Lu-octreotate: |  |  |
| Total subjects affected by non-serious adverse events               |                              |  |  |
| subjects affected / exposed   | 37 / 37 (100.00%)            |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                              |  |  |
| Skin papilloma  |                              |  |  |
| subjects affected / exposed   | 1 / 37 (2.70%)               |  |  |
| occurrences (all)   | 1                            |  |  |
| Vascular disorders  |                              |  |  |
| Flushing  |                              |  |  |
| subjects affected / exposed   | 4 / 37 (10.81%)              |  |  |
| occurrences (all)   | 9                            |  |  |
| Hot flush   |                              |  |  |
| subjects affected / exposed   | 2 / 37 (5.41%)               |  |  |
| occurrences (all)   | 2                            |  |  |
| Hypertension  |                              |  |  |
| subjects affected / exposed   | 1 / 37 (2.70%)               |  |  |
| occurrences (all)   | 1                            |  |  |
| Hypotension   |                              |  |  |
| subjects affected / exposed   | 1 / 37 (2.70%)               |  |  |
| occurrences (all)   | 1                            |  |  |
| General disorders and administration site conditions                |                              |  |  |
| Catheter site pain  |                              |  |  |
| subjects affected / exposed   | 1 / 37 (2.70%)               |  |  |
| occurrences (all)   | 1                            |  |  |
| Catheter site pruritus  |                              |  |  |
| subjects affected / exposed   | 1 / 37 (2.70%)               |  |  |
| occurrences (all)   | 1                            |  |  |
| Fatigue   |                              |  |  |
| subjects affected / exposed   | 19 / 37 (51.35%)             |  |  |
| occurrences (all)   | 22                           |  |  |
| Induration  |                              |  |  |
| subjects affected / exposed   | 1 / 37 (2.70%)               |  |  |
| occurrences (all)   | 1                            |  |  |
| Infusion site extravasation   |                              |  |  |
| subjects affected / exposed   | 1 / 37 (2.70%)               |  |  |
| occurrences (all)   | 1                            |  |  |

|  |                      |  |  |
|--|----------------------|--|--|
| Malaise<br>subjects affected / exposed<br>occurrences (all)  | 1 / 37 (2.70%)<br>1  |  |  |
| Oedema<br>subjects affected / exposed<br>occurrences (all)   | 2 / 37 (5.41%)<br>2  |  |  |
| Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)  | 2 / 37 (5.41%)<br>2  |  |  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)  | 4 / 37 (10.81%)<br>4 |  |  |
| Reproductive system and breast disorders<br>Benign prostatic hyperplasia<br>subjects affected / exposed<br>occurrences (all) | 1 / 37 (2.70%)<br>1  |  |  |
| Prostatitis<br>subjects affected / exposed<br>occurrences (all)  | 1 / 37 (2.70%)<br>1  |  |  |
| Vaginal haemorrhage<br>subjects affected / exposed<br>occurrences (all)  | 1 / 37 (2.70%)<br>1  |  |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)                 | 2 / 37 (5.41%)<br>2  |  |  |
| Hiccups<br>subjects affected / exposed<br>occurrences (all)  | 3 / 37 (8.11%)<br>5  |  |  |
| Hypoventilation<br>subjects affected / exposed<br>occurrences (all)  | 1 / 37 (2.70%)<br>1  |  |  |
| Pleural effusion<br>subjects affected / exposed<br>occurrences (all)   | 3 / 37 (8.11%)<br>4  |  |  |
| Wheezing   |                      |  |  |



|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                           | 2 / 37 (5.41%)   |  |  |
| occurrences (all)                                     | 2                |  |  |
| Psychiatric disorders                                 |                  |  |  |
| Anxiety   |                  |  |  |
| subjects affected / exposed                           | 2 / 37 (5.41%)   |  |  |
| occurrences (all)                                     | 2                |  |  |
| Depression  |                  |  |  |
| subjects affected / exposed                           | 1 / 37 (2.70%)   |  |  |
| occurrences (all)                                     | 1                |  |  |
| Insomnia  |                  |  |  |
| subjects affected / exposed                           | 1 / 37 (2.70%)   |  |  |
| occurrences (all)                                     | 4                |  |  |
| Investigations  |                  |  |  |
| Alanine aminotransferase increased                    |                  |  |  |
| subjects affected / exposed                           | 10 / 37 (27.03%) |  |  |
| occurrences (all)                                     | 16               |  |  |
| Activated partial thromboplastin time ratio increased |                  |  |  |
| subjects affected / exposed                           | 1 / 37 (2.70%)   |  |  |
| occurrences (all)                                     | 1                |  |  |
| Aspartate aminotransferase increased                  |                  |  |  |
| subjects affected / exposed                           | 9 / 37 (24.32%)  |  |  |
| occurrences (all)                                     | 17               |  |  |
| Blood alkaline phosphatase increased                  |                  |  |  |
| subjects affected / exposed                           | 7 / 37 (18.92%)  |  |  |
| occurrences (all)                                     | 11               |  |  |
| Blood bilirubin increased                             |                  |  |  |
| subjects affected / exposed                           | 1 / 37 (2.70%)   |  |  |
| occurrences (all)                                     | 1                |  |  |
| Blood cholesterol increased                           |                  |  |  |
| subjects affected / exposed                           | 1 / 37 (2.70%)   |  |  |
| occurrences (all)                                     | 1                |  |  |
| Blood lactate dehydrogenase increased                 |                  |  |  |
| subjects affected / exposed                           | 12 / 37 (32.43%) |  |  |
| occurrences (all)                                     | 22               |  |  |
| Gamma-glutamyltransferase                             |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| increased   |                  |  |  |
| subjects affected / exposed                               | 1 / 37 (2.70%)   |  |  |
| occurrences (all)   | 2                |  |  |
| International normalised ratio increased                  |                  |  |  |
| subjects affected / exposed                               | 1 / 37 (2.70%)   |  |  |
| occurrences (all)   | 2                |  |  |
| Lymphocyte count decreased                                |                  |  |  |
| subjects affected / exposed                               | 24 / 37 (64.86%) |  |  |
| occurrences (all)   | 32               |  |  |
| Lymphocyte count increased                                |                  |  |  |
| subjects affected / exposed                               | 1 / 37 (2.70%)   |  |  |
| occurrences (all)   | 1                |  |  |
| Neutrophil count decreased                                |                  |  |  |
| subjects affected / exposed                               | 4 / 37 (10.81%)  |  |  |
| occurrences (all)   | 6                |  |  |
| N-terminal prohormone brain natriuretic peptide increased |                  |  |  |
| subjects affected / exposed                               | 1 / 37 (2.70%)   |  |  |
| occurrences (all)   | 1                |  |  |
| Platelet count decreased                                  |                  |  |  |
| subjects affected / exposed                               | 19 / 37 (51.35%) |  |  |
| occurrences (all)   | 41               |  |  |
| Weight decreased  |                  |  |  |
| subjects affected / exposed                               | 2 / 37 (5.41%)   |  |  |
| occurrences (all)   | 2                |  |  |
| Weight increased  |                  |  |  |
| subjects affected / exposed                               | 1 / 37 (2.70%)   |  |  |
| occurrences (all)   | 1                |  |  |
| White blood cell count decreased                          |                  |  |  |
| subjects affected / exposed                               | 12 / 37 (32.43%) |  |  |
| occurrences (all)   | 23               |  |  |
| Injury, poisoning and procedural complications            |                  |  |  |
| Contusion   |                  |  |  |
| subjects affected / exposed                               | 1 / 37 (2.70%)   |  |  |
| occurrences (all)   | 1                |  |  |
| Spinal compression fracture                               |                  |  |  |

|  |   |  |  |
|--|---|--|--|
| subjects affected / exposed<br>occurrences (all)   | 1 / 37 (2.70%)<br>1   |  |  |
| Congenital, familial and genetic disorders<br>Phimosis<br>subjects affected / exposed<br>occurrences (all)   | 1 / 37 (2.70%)<br>1   |  |  |
| Cardiac disorders<br>Mitral valve incompetence<br>subjects affected / exposed<br>occurrences (all)<br><br>Tricuspid valve sclerosis<br>subjects affected / exposed<br>occurrences (all)<br><br>Ventricular arrhythmia<br>subjects affected / exposed<br>occurrences (all)  | 1 / 37 (2.70%)<br>1<br><br>1 / 37 (2.70%)<br>1<br><br>1 / 37 (2.70%)<br>1   |  |  |
| Nervous system disorders<br>Carpal tunnel syndrome<br>subjects affected / exposed<br>occurrences (all)<br><br>Dysgeusia<br>subjects affected / exposed<br>occurrences (all)<br><br>Headache<br>subjects affected / exposed<br>occurrences (all)<br><br>Paresis<br>subjects affected / exposed<br>occurrences (all)<br><br>Presyncope<br>subjects affected / exposed<br>occurrences (all) | 1 / 37 (2.70%)<br>1<br><br>4 / 37 (10.81%)<br>6<br><br>7 / 37 (18.92%)<br>7<br><br>1 / 37 (2.70%)<br>1<br><br>2 / 37 (5.41%)<br>2 |  |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)  | 23 / 37 (62.16%)<br>47  |  |  |

|  |  |  |  |
|--|--|--|--|
| Hilar lymphadenopathy<br>subjects affected / exposed<br>occurrences (all)  | 1 / 37 (2.70%)<br>1  |  |  |
| Leukocytosis<br>subjects affected / exposed<br>occurrences (all)   | 2 / 37 (5.41%)<br>2  |  |  |
| Ear and labyrinth disorders<br>Tinnitus<br>subjects affected / exposed<br>occurrences (all)<br><br>Vertigo<br>subjects affected / exposed<br>occurrences (all)   | 1 / 37 (2.70%)<br>1<br><br>4 / 37 (10.81%)<br>5  |  |  |
| Eye disorders<br>Cataract<br>subjects affected / exposed<br>occurrences (all)<br><br>Eye disorder<br>subjects affected / exposed<br>occurrences (all)<br><br>Glaucoma<br>subjects affected / exposed<br>occurrences (all)<br><br>Visual field defect<br>subjects affected / exposed<br>occurrences (all)<br><br>Visual impairment<br>subjects affected / exposed<br>occurrences (all)<br><br>Vitreous detachment<br>subjects affected / exposed<br>occurrences (all) | 1 / 37 (2.70%)<br>1<br><br>1 / 37 (2.70%)<br>1<br><br>1 / 37 (2.70%)<br>1<br><br>1 / 37 (2.70%)<br>1<br><br>1 / 37 (2.70%)<br>1<br><br>1 / 37 (2.70%)<br>1 |  |  |
| Gastrointestinal disorders<br>Abdominal pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Abdominal pain lower   | 6 / 37 (16.22%)<br>9   |  |  |

|                                  |                  |  |  |
|----------------------------------|------------------|--|--|
| subjects affected / exposed      | 1 / 37 (2.70%)   |  |  |
| occurrences (all)                | 1                |  |  |
| Abdominal pain upper             |                  |  |  |
| subjects affected / exposed      | 5 / 37 (13.51%)  |  |  |
| occurrences (all)                | 8                |  |  |
| Chronic gastritis                |                  |  |  |
| subjects affected / exposed      | 1 / 37 (2.70%)   |  |  |
| occurrences (all)                | 1                |  |  |
| Constipation                     |                  |  |  |
| subjects affected / exposed      | 9 / 37 (24.32%)  |  |  |
| occurrences (all)                | 11               |  |  |
| Diarrhoea                        |                  |  |  |
| subjects affected / exposed      | 10 / 37 (27.03%) |  |  |
| occurrences (all)                | 12               |  |  |
| Diverticulum                     |                  |  |  |
| subjects affected / exposed      | 1 / 37 (2.70%)   |  |  |
| occurrences (all)                | 1                |  |  |
| Dry mouth                        |                  |  |  |
| subjects affected / exposed      | 1 / 37 (2.70%)   |  |  |
| occurrences (all)                | 1                |  |  |
| Dyspepsia                        |                  |  |  |
| subjects affected / exposed      | 1 / 37 (2.70%)   |  |  |
| occurrences (all)                | 1                |  |  |
| Dysphagia                        |                  |  |  |
| subjects affected / exposed      | 2 / 37 (5.41%)   |  |  |
| occurrences (all)                | 2                |  |  |
| Gastric ulcer                    |                  |  |  |
| subjects affected / exposed      | 1 / 37 (2.70%)   |  |  |
| occurrences (all)                | 1                |  |  |
| Gastritis                        |                  |  |  |
| subjects affected / exposed      | 1 / 37 (2.70%)   |  |  |
| occurrences (all)                | 1                |  |  |
| Gastrointestinal pain            |                  |  |  |
| subjects affected / exposed      | 2 / 37 (5.41%)   |  |  |
| occurrences (all)                | 2                |  |  |
| Gastrooesophageal reflux disease |                  |  |  |

|  |                  |  |  |
|--|------------------|--|--|
| subjects affected / exposed            | 1 / 37 (2.70%)   |  |  |
| occurrences (all)                      | 1                |  |  |
| Haemorrhoidal haemorrhage              |                  |  |  |
| subjects affected / exposed            | 2 / 37 (5.41%)   |  |  |
| occurrences (all)                      | 2                |  |  |
| Hiatus hernia                          |                  |  |  |
| subjects affected / exposed            | 1 / 37 (2.70%)   |  |  |
| occurrences (all)                      | 1                |  |  |
| Intestinal obstruction                 |                  |  |  |
| subjects affected / exposed            | 1 / 37 (2.70%)   |  |  |
| occurrences (all)                      | 1                |  |  |
| Nausea                                 |                  |  |  |
| subjects affected / exposed            | 15 / 37 (40.54%) |  |  |
| occurrences (all)                      | 28               |  |  |
| Reflux gastritis                       |                  |  |  |
| subjects affected / exposed            | 1 / 37 (2.70%)   |  |  |
| occurrences (all)                      | 1                |  |  |
| Vomiting                               |                  |  |  |
| subjects affected / exposed            | 11 / 37 (29.73%) |  |  |
| occurrences (all)                      | 18               |  |  |
| Hepatobiliary disorders                |                  |  |  |
| Ocular icterus                         |                  |  |  |
| subjects affected / exposed            | 1 / 37 (2.70%)   |  |  |
| occurrences (all)                      | 1                |  |  |
| Skin and subcutaneous tissue disorders |                  |  |  |
| Alopecia                               |                  |  |  |
| subjects affected / exposed            | 17 / 37 (45.95%) |  |  |
| occurrences (all)                      | 23               |  |  |
| Dermatitis allergic                    |                  |  |  |
| subjects affected / exposed            | 1 / 37 (2.70%)   |  |  |
| occurrences (all)                      | 1                |  |  |
| Eczema                                 |                  |  |  |
| subjects affected / exposed            | 1 / 37 (2.70%)   |  |  |
| occurrences (all)                      | 1                |  |  |
| Erythema                               |                  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 37 (2.70%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Hirsutism                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 37 (2.70%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Hyperhidrosis                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 37 (2.70%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Pruritus  |                 |  |  |
| subjects affected / exposed                     | 2 / 37 (5.41%)  |  |  |
| occurrences (all)                               | 4               |  |  |
| Urticaria                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 37 (2.70%)  |  |  |
| occurrences (all)                               | 3               |  |  |
| Renal and urinary disorders                     |                 |  |  |
| Chronic kidney disease                          |                 |  |  |
| subjects affected / exposed                     | 3 / 37 (8.11%)  |  |  |
| occurrences (all)                               | 3               |  |  |
| Micturition urgency                             |                 |  |  |
| subjects affected / exposed                     | 1 / 37 (2.70%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Pollakiuria                                     |                 |  |  |
| subjects affected / exposed                     | 1 / 37 (2.70%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Urethral stenosis                               |                 |  |  |
| subjects affected / exposed                     | 1 / 37 (2.70%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Endocrine disorders                             |                 |  |  |
| Hypothyroidism                                  |                 |  |  |
| subjects affected / exposed                     | 3 / 37 (8.11%)  |  |  |
| occurrences (all)                               | 3               |  |  |
| Musculoskeletal and connective tissue disorders |                 |  |  |
| Arthralgia                                      |                 |  |  |
| subjects affected / exposed                     | 5 / 37 (13.51%) |  |  |
| occurrences (all)                               | 5               |  |  |
| Back pain                                       |                 |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 4 / 37 (10.81%) |  |  |
| occurrences (all)           | 4               |  |  |
| Bone pain                   |                 |  |  |
| subjects affected / exposed | 1 / 37 (2.70%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Joint stiffness             |                 |  |  |
| subjects affected / exposed | 1 / 37 (2.70%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Myalgia                     |                 |  |  |
| subjects affected / exposed | 1 / 37 (2.70%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Pain in extremity           |                 |  |  |
| subjects affected / exposed | 3 / 37 (8.11%)  |  |  |
| occurrences (all)           | 3               |  |  |
| Periarthritis               |                 |  |  |
| subjects affected / exposed | 1 / 37 (2.70%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Spinal pain                 |                 |  |  |
| subjects affected / exposed | 1 / 37 (2.70%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Infections and infestations |                 |  |  |
| Bronchitis                  |                 |  |  |
| subjects affected / exposed | 4 / 37 (10.81%) |  |  |
| occurrences (all)           | 4               |  |  |
| Folliculitis                |                 |  |  |
| subjects affected / exposed | 1 / 37 (2.70%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Gastroenteritis             |                 |  |  |
| subjects affected / exposed | 3 / 37 (8.11%)  |  |  |
| occurrences (all)           | 3               |  |  |
| Infection                   |                 |  |  |
| subjects affected / exposed | 1 / 37 (2.70%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Otitis media                |                 |  |  |
| subjects affected / exposed | 1 / 37 (2.70%)  |  |  |
| occurrences (all)           | 1               |  |  |



|   |                      |  |  |
|---|----------------------|--|--|
| Pneumonia mycoplasmal<br>subjects affected / exposed<br>occurrences (all)             | 1 / 37 (2.70%)<br>1  |  |  |
| Post procedural infection<br>subjects affected / exposed<br>occurrences (all)         | 1 / 37 (2.70%)<br>1  |  |  |
| Respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)       | 1 / 37 (2.70%)<br>1  |  |  |
| Skin infection<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 37 (2.70%)<br>1  |  |  |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 4 / 37 (10.81%)<br>6 |  |  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)           | 2 / 37 (5.41%)<br>2  |  |  |
| Wound infection<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 37 (2.70%)<br>1  |  |  |
| Metabolism and nutrition disorders  |                      |  |  |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)                | 2 / 37 (5.41%)<br>3  |  |  |
| Hypercalcaemia<br>subjects affected / exposed<br>occurrences (all)                    | 2 / 37 (5.41%)<br>3  |  |  |
| Hypercholesterolaemia<br>subjects affected / exposed<br>occurrences (all)             | 1 / 37 (2.70%)<br>1  |  |  |
| Hyperkalaemia<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 37 (2.70%)<br>1  |  |  |
| Hyperuricaemia  |                      |  |  |

|                             |                |  |  |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 1 / 37 (2.70%) |  |  |
| occurrences (all)           | 2              |  |  |
| Hypocalcaemia               |                |  |  |
| subjects affected / exposed | 1 / 37 (2.70%) |  |  |
| occurrences (all)           | 1              |  |  |
| Iron deficiency             |                |  |  |
| subjects affected / exposed | 1 / 37 (2.70%) |  |  |
| occurrences (all)           | 1              |  |  |
| Vitamin D deficiency        |                |  |  |
| subjects affected / exposed | 1 / 37 (2.70%) |  |  |
| occurrences (all)           | 1              |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                                    |
|-------------------|--|
| 20 December 2012  | protocol v2.0<br>ICF v2.0                    |
| 27 May 2013       | Protocol v3.0<br>ICF v3.1                    |
| 07 November 2013  | Protocol v3.3<br>ICF v3.1                    |
| 05 June 2014      | Protocol v4.0<br>ICF v4.0                    |
| 24 June 2015      | Protocol v5.0<br>ICF v5.1                    |
| 17 September 2015 | Protocol v6.0<br>ICF v6.0                    |
| 22 October 2015   | Addendum A & B                               |
| 28 September 2016 | Protocol v7.2<br>ICF v7.0<br>Addendum C v1.0 |
| 22 June 2017      | RSI change                                   |
| 06 December 2018  | ICF v8.0<br>GDPR information letter          |
| 17 June 2021      | Protocol v8.0                                |
| 21 October 2021   | Institut Jules Bordet move                   |
| 09 March 2022     | new insurer                                  |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported