Clinical trial results:
The LuMEn 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
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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 177Lu-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

Arm title	77Lu-octreotate

Arm description:

This treatment consisted of 177Lu-octreotate injections(4 cycles) in fixed activities of 7,4GBq (200 mCi) (±5%) each, given 12 weeks (±1week) 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) (±5%) each, given 12 weeks (±1week) 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 (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	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 Units: Subjects			
Yes	12	12	
No	25	25	
site of metastases : pancreas Units: Subjects			
Yes	3	3	
No	34	34	
site of metastasis: lung Units: Subjects			
Yes	2	2	
No	35	35	
site of metastases: other (pleural, adrenal, ovarium, mesentery/pelvic) Units: Subjects			
Yes	6	6	
No	31	31	
symptoms: diarrhoea Units: Subjects			
Yes	16	16	
No	21	21	
symptoms: pain Units: Subjects			
Yes	15	15	
No	22	22	
symptoms: fatigue Units: Subjects			
Yes	11	11	
No	26	26	
symptoms: flushes Units: Subjects			
Yes	9	9	
No	28	28	
No symptoms Units: Subjects			
Yes	12	12	
no	25	25	
Positive 18FDG-PET/CT Units: Subjects			
Yes	15	15	
No	22	22	
surgery (including primary tumour resection) Units: Subjects			
Yes	27	27	
No	10	10	
SSAs Units: Subjects			
Yes	36	36	
No	1	1	

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

End points

End points reporting groups

Reporting group title	77Lu-octreotate

Reporting group description:

This treatment consisted of 177Lu-octreotate injections(4 cycles) in fixed activities of 7,4GBq (200 mCi) (±5%) each, given 12 weeks (±1week) 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)[1]

End point description:

116 target lesions. 84 out of 116 were considered evaluable.
1) 18FDG PET/CT imaging: No significant association with the lesion morphological outcome was observed for any of the 18FDG PET baseline parameters.
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.
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:

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[2]			
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:

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[3]			
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:

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.

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[4]			
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 (>=22mm) 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)

End point values	77Lu-octreotate			
Subject group type	Reporting group			
Number of subjects analysed	37[5]			
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.

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

Notes:

[6] - treated patients

Statistical analyses

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 %

Non-serious adverse events	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 occurrences (all)	 1 / 37 (2.70%) 1		
Vascular disorders Flushing subjects affected / exposed occurrences (all) Hot flush subjects affected / exposed occurrences (all) Hypertension subjects affected / exposed occurrences (all) Hypotension subjects affected / exposed occurrences (all)	 4 / 37 (10.81%) 9 2 / 37 (5.41%) 2 1 / 37 (2.70%) 1 1 / 37 (2.70%) 1		
General disorders and administration site conditions Catheter site pain subjects affected / exposed occurrences (all) Catheter site pruritus subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Induration subjects affected / exposed occurrences (all) Infusion site extravasation subjects affected / exposed occurrences (all)	 1 / 37 (2.70%) 1 1 / 37 (2.70%) 1 19 / 37 (51.35%) 22 1 / 37 (2.70%) 1 1 / 37 (2.70%) 1		

Malaise			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Oedema			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Oedema peripheral			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	4 / 37 (10.81%)		
occurrences (all)	4		
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Prostatitis			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Vaginal haemorrhage			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Hiccups			
subjects affected / exposed	3 / 37 (8.11%)		
occurrences (all)	5		
Hypoventilation			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Pleural effusion			
subjects affected / exposed	3 / 37 (8.11%)		
occurrences (all)	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	1 / 37 (2.70%)		
occurrences (all)	1		
Congenital, familial and genetic disorders			
Phimosis			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Cardiac disorders			
Mitral valve incompetence			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Tricuspid valve sclerosis			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Ventricular arrhythmia			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Dysgeusia			
subjects affected / exposed	4 / 37 (10.81%)		
occurrences (all)	6		
Headache			
subjects affected / exposed	7 / 37 (18.92%)		
occurrences (all)	7		
Paresis			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Presyncope			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	23 / 37 (62.16%)		
occurrences (all)	47		

Hilar lymphadenopathy subjects affected / exposed occurrences (all) Leukocytosis subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1 2 / 37 (5.41%) 2		
Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all) Vertigo subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1 4 / 37 (10.81%) 5		
Eye disorders Cataract subjects affected / exposed occurrences (all) Eye disorder subjects affected / exposed occurrences (all) Glaucoma subjects affected / exposed occurrences (all) Visual field defect subjects affected / exposed occurrences (all) Visual impairment subjects affected / exposed occurrences (all) Vitreous detachment subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1 1 / 37 (2.70%) 1 1 / 37 (2.70%) 1 1 / 37 (2.70%) 1 1 / 37 (2.70%) 1 1 / 37 (2.70%) 1		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain lower	6 / 37 (16.22%) 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 occurrences (all) Hirsutism subjects affected / exposed occurrences (all) Hyperhidrosis subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Urticaria subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1 1 / 37 (2.70%) 1 1 / 37 (2.70%) 1 2 / 37 (5.41%) 4 1 / 37 (2.70%) 3		
Renal and urinary disorders Chronic kidney disease subjects affected / exposed occurrences (all) Micturition urgency subjects affected / exposed occurrences (all) Pollakiuria subjects affected / exposed occurrences (all) Urethral stenosis subjects affected / exposed occurrences (all)	 3 / 37 (8.11%) 3 1 / 37 (2.70%) 1 1 / 37 (2.70%) 1 1 / 37 (2.70%) 1		
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	 3 / 37 (8.11%) 3		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain	 5 / 37 (13.51%) 5		

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			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Post procedural infection			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Respiratory tract infection			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Skin infection			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	4 / 37 (10.81%)		
occurrences (all)	6		
Urinary tract infection			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Wound infection			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	3		
Hypercalcaemia			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	3		
Hypercholesterolaemia			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Hyperkalaemia			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	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 ICF v2.0
27 May 2013	Protocol v3.0 ICF v3.1
07 November 2013	Protocol v3.3 ICF v3.1
05 June 2014	Protocol v4.0 ICF v4.0
24 June 2015	Protocol v5.0 ICF v5.1
17 September 2015	Protocol v6.0 ICF v6.0
22 October 2015	Addendum A & B
28 September 2016	Protocol v7.2 ICF v7.0 Addendum C v1.0
22 June 2017	RSI change
06 December 2018	ICF v8.0 GDPR information letter
17 June 2021	Protocol v8.0
21 October 2021	Institut Jules Bordet move
09 March 2022	new insurer

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported