



Clinical trial results:

A phase II prospective imaging study evaluating the utility of pre-treatment zirconium-89 labelled trastuzumab PET/CT and an early FDG-PET/CT response to identify patients with advanced HER-2 positive breast cancer unlikely to benefit from a novel anti-HER2 therapy: T-DM1 Summary

EudraCT number	2011-005437-39
Trial protocol	BE NL
Global end of trial date	09 April 2024

Results information

Result version number	v1 (current)
This version publication date	10 August 2025
First version publication date	10 August 2025
Summary attachment (see zip file)	ZEPHIR_Final_Study_Report (201100543739-final_study_report.pdf)

Trial information

Trial identification

Sponsor protocol code	IJBMNTDM1
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01565200
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Institut Jules Bordet
Sponsor organisation address	Rue Meylemeersch 90,, Anderlecht, Belgium, 1070
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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	08 December 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 July 2017
Global end of trial reached?	Yes
Global end of trial date	09 April 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to show, on a lesion-based analysis, that pre-treatment 89Zr-trastuzumab PET/CT is able to select lesions not responding morphologically from treatment with T-DM1 (applying RECIST 1.0 criteria).

Protection of trial subjects:

To ensure patient safety during treatment, in the event of treatment related toxicity, a dose delay or dose reduction to 3 or 2.4 mg/kg was allowed. Additionally, concomitant therapy, such as: bisphosphonates and other bone supportive agents, palliative radiotherapy for painful bone metastases and gamma knife or radiotherapy for symptomatic brain metastases, was allowed as supportive measure.

Background therapy:

NA

Evidence for comparator:

NA

Actual start date of recruitment	05 March 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 41
Country: Number of subjects enrolled	Belgium: 49
Worldwide total number of subjects	90
EEA total number of subjects	90

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)	72
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between 07/05/2012 and 24/02/2017, subjects were recruited in 5 participating sites in 2 countries (Belgium and the Netherlands).

Pre-assignment

Screening details:

Once informed consent was signed, inclusion and exclusion criteria were double checked to identify any screening failure. They were reported in the trial registration tool.

Period 1

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

Blinding implementation details:

Roles blinded : Investigators for imaging results.

The nuclearist physicians kept their assessments confidential until the analysis of the trial results.

Arms

Arm title	Not applicable as there is only one cohort in this study
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Arm description:

The treatment was approved in the indication (TDM1).

The search about the predictive value of HER2 PET and early FDGPET on treatment efficacy was investigated in a single arm study

Arm type	Experimental
Investigational medicinal product name	trastuzumab
Investigational medicinal product code	L01XC03
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Coinjection of 50 mg trastuzumab and 37 MBq $\pm$ 10% 89Zrtrastuzumab

Investigational medicinal product name	TDM1
Investigational medicinal product code	
Other name	Kadcyla, Trastuzumab Emtansine
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

TDM1: 3.6 mg/kg, IV, every 3 weeks until disease progression

Investigational medicinal product name	89Zr-SucDF-Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Coinjection of 50 mg trastuzumab and 37 MBq $\pm$ 10% 89Zrtrastuzumab

Number of subjects in period 1	Not applicable as there is only one cohort in this study
Started	90
Completed	83
Not completed	7
As per protocol	7

Baseline characteristics

Reporting groups

Reporting group title	Overall trial
Reporting group description: -	

Reporting group values	Overall trial	Total	
Number of subjects	90	90	
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)	72	72	
From 65-84 years	18	18	
85 years and over	0	0	
Age continuous			
Units: years			
median	54		
full range (min-max)	30 to 78	-	
Gender categorical			
Units: Subjects			
Female	90	90	
Male	0	0	
ECOG			
Units: Subjects			
Zero	46	46	
One	44	44	
Disease type at screening			
Units: Subjects			
Visceral	84	84	
Non-visceral	6	6	
History of brain metastases			
Units: Subjects			
Yes	20	20	
No	70	70	
HER2-positivity based on primary tumor			
82 confirmed by reference lab			
Units: Subjects			
FISH+ only	4	4	
IHC 2+ with FISH+	11	11	
IHC 3+ with FISH+	42	42	
IHC 3+ without FISH+	27	27	
Not concerned	6	6	

HER2positivity based on metastatic biopsy			
All confirmed by reference lab			
Units: Subjects			
FISH+ only	0	0	
IHC 2+ with FISH+	3	3	
IHC 3+ with FISH+	2	2	
IHC 3+ without FISH+	1	1	
Not concerned or not analysed	84	84	
Hormone receptor status			
Units: Subjects			
ER+ or PR+ or both	63	63	
ER- and PR-	27	27	
Prior systemic therapies for advanced disease			
Details in the attached final report document			
Units: Subjects			
Yes	83	83	
No	7	7	

End points

End points reporting groups

Reporting group title	Not applicable as there is only one cohort in this study
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Reporting group description:

The treatment was approved in the indication (TDM1).

The search about the predictive value of HER2 PET and early FDGPET on treatment efficacy was investigated in a single arm study

Primary: Analyse of response using a lesionbased analysis

End point title	Analyse of response using a lesionbased analysis ^[1]
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End point description:

Our main objective was to evaluate the ability of HER2 PET/CT to predict, before initiation of treatment, tumor lesions unlikely to respond anatomically to TDM1. The ability of HER2 PET/CT to predict metabolic response after three cycles of TDM1 was also explored. In addition, we analyzed how an early FDG PET/CT, alone or combined with the pretreatment HER2 PET/CT, can identify tumor lesions that will not respond (anatomically and metabolically) after three TDM1 cycles.

End point type	Primary
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End point timeframe:

Entire study

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: As this is a single arm study with no comparison, it was not possible to include a statistical analysis without an error message.

For full statistical analysis, please see document hereto attached, section 5. End points.

End point values	Not applicable as there is only one cohort in this study			
Subject group type	Reporting group			
Number of subjects analysed	83			
Units: lesions				
number (not applicable)	388			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

After informed consent, but prior to initiation of study medications , only SAEs caused by a protocol mandated intervention were collected. From initiation of study medications until 30 days after the last T-DM1 dose, all AEs and SAEs were collected.

Adverse event reporting additional description:

Progression of underlying malignancy will not be reported as an adverse event if it is clearly consistent with the suspected progression of the underlying cancer as defined by RECIST 1.1 or FDG PET/CT (after 3 cycles of TDM1). See full document for more details

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	27.1

Reporting groups

Reporting group title	Safety analysis for all treated subjects
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Reporting group description:

All subjects included in the trial

Serious adverse events	Safety analysis for all treated subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 90 (22.22%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour haemorrhage			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure chronic			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pericardial effusion			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Supraventricular tachycardia			

subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cognitive disorder			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	3 / 90 (3.33%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Drug hypersensitivity			

subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypersensitivity			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Mental disorder			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Anal abscess			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bacteraemia			

subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Soft tissue infection			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypercalcaemia			

subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety analysis for all treated subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	86 / 90 (95.56%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemangioma			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences (all)	2		
Tumour pain			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Vascular disorders			
Arteriosclerosis			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Circulatory collapse			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Haematoma			
subjects affected / exposed	5 / 90 (5.56%)		
occurrences (all)	9		
Haemorrhage			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences (all)	3		
Hot flush			
subjects affected / exposed	6 / 90 (6.67%)		
occurrences (all)	12		
Hypertension			
subjects affected / exposed	6 / 90 (6.67%)		
occurrences (all)	8		

Hypotension			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Lymphoedema			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Phlebitis			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences (all)	2		
White coat hypertension			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Catheter site inflammation			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Chest pain			
subjects affected / exposed	4 / 90 (4.44%)		
occurrences (all)	4		
Chills			
subjects affected / exposed	26 / 90 (28.89%)		
occurrences (all)	44		
Fatigue			
subjects affected / exposed	53 / 90 (58.89%)		
occurrences (all)	292		
Gait disturbance			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences (all)	2		
Hypothermia			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Influenza like illness			

subjects affected / exposed	19 / 90 (21.11%)		
occurrences (all)	24		
Injection site nodule			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Localised oedema			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Malaise			
subjects affected / exposed	9 / 90 (10.00%)		
occurrences (all)	14		
Mucosal dryness			
subjects affected / exposed	3 / 90 (3.33%)		
occurrences (all)	5		
Mucosal inflammation			
subjects affected / exposed	7 / 90 (7.78%)		
occurrences (all)	7		
Oedema			
subjects affected / exposed	6 / 90 (6.67%)		
occurrences (all)	7		
Oedema peripheral			
subjects affected / exposed	13 / 90 (14.44%)		
occurrences (all)	23		
Pain			
subjects affected / exposed	14 / 90 (15.56%)		
occurrences (all)	16		
Pyrexia			
subjects affected / exposed	21 / 90 (23.33%)		
occurrences (all)	37		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Mite allergy			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		

Folliculitis subjects affected / exposed occurrences (all)	1 / 90 (1.11%) 1		
Reproductive system and breast disorders			
Adnexa uteri pain subjects affected / exposed occurrences (all)	1 / 90 (1.11%) 1		
Breast pain subjects affected / exposed occurrences (all)	2 / 90 (2.22%) 1		
Genital atrophy subjects affected / exposed occurrences (all)	1 / 90 (1.11%) 1		
Genital burning sensation subjects affected / exposed occurrences (all)	1 / 90 (1.11%) 1		
Genital haemorrhage subjects affected / exposed occurrences (all)	1 / 90 (1.11%) 1		
Vaginal haemorrhage subjects affected / exposed occurrences (all)	2 / 90 (2.22%) 2		
Vulvovaginal dryness subjects affected / exposed occurrences (all)	1 / 90 (1.11%) 1		
Respiratory, thoracic and mediastinal disorders			
Bronchial obstruction subjects affected / exposed occurrences (all)	1 / 90 (1.11%) 1		
Cough subjects affected / exposed occurrences (all)	13 / 90 (14.44%) 21		
Dysphonia subjects affected / exposed occurrences (all)	4 / 90 (4.44%) 5		
Dyspnoea			

subjects affected / exposed	14 / 90 (15.56%)		
occurrences (all)	21		
Dyspnoea exertional			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	28 / 90 (31.11%)		
occurrences (all)	92		
Haemoptysis			
subjects affected / exposed	3 / 90 (3.33%)		
occurrences (all)	4		
Hypersensitivity pneumonitis			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Interstitial lung disease			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Nasal congestion			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Nasal obstruction			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Nasal ulcer			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	3		
Oropharyngeal pain			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Rhinitis allergic			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Rhinorrhoea			
subjects affected / exposed	3 / 90 (3.33%)		
occurrences (all)	5		
Sinus disorder			

subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Sinus pain			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Sneezing			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	4 / 90 (4.44%)		
occurrences (all)	4		
Confusional state			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Depression			
subjects affected / exposed	6 / 90 (6.67%)		
occurrences (all)	7		
Hallucination, visual			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Sleep disorder			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	23 / 90 (25.56%)		
occurrences (all)	32		
Aspartate aminotransferase increased			
subjects affected / exposed	28 / 90 (31.11%)		
occurrences (all)	36		
Blood alkaline phosphatase increased			

subjects affected / exposed	10 / 90 (11.11%)		
occurrences (all)	14		
Blood bilirubin increased			
subjects affected / exposed	4 / 90 (4.44%)		
occurrences (all)	5		
Blood cholesterol increased			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Blood creatinine increased			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Ejection fraction decreased			
subjects affected / exposed	8 / 90 (8.89%)		
occurrences (all)	10		
Gamma-glutamyltransferase increased			
subjects affected / exposed	21 / 90 (23.33%)		
occurrences (all)	27		
Heart rate increased			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Menstruation normal			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Neutrophil count decreased			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences (all)	2		
Platelet count decreased			
subjects affected / exposed	15 / 90 (16.67%)		
occurrences (all)	32		
Serum ferritin decreased			

subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Allergic transfusion reaction			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Contusion			
subjects affected / exposed	9 / 90 (10.00%)		
occurrences (all)	23		
Ear canal injury			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Fall			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	2		
Foot fracture			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Foreign body			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Fracture			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Infusion related reaction			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences (all)	2		
Limb injury			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Procedural pain			

subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Radiation neuropathy			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Radiation skin injury			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Scar			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Scratch			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Wrist fracture			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences (all)	2		
Cardiac disorders			
Extrasystoles			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences (all)	2		
Palpitations			
subjects affected / exposed	4 / 90 (4.44%)		
occurrences (all)	12		
Ventricular extracystoles			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences (all)	2		
Nervous system disorders			
Amnesia			
subjects affected / exposed	3 / 90 (3.33%)		
occurrences (all)	3		
Aphasia			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Ataxia			

subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Balance disorder			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Burning sensation			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Carpal tunnel syndrome			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences (all)	2		
Coordination abnormal			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Disturbance in attention			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	11 / 90 (12.22%)		
occurrences (all)	27		
Dyaesthesia			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Dysgeusia			
subjects affected / exposed	9 / 90 (10.00%)		
occurrences (all)	9		
Headache			
subjects affected / exposed	34 / 90 (37.78%)		
occurrences (all)	202		
Hypoaesthesia			
subjects affected / exposed	3 / 90 (3.33%)		
occurrences (all)	3		
Nervous system disorder			
subjects affected / exposed	3 / 90 (3.33%)		
occurrences (all)	3		
Neuropathy peripheral			

subjects affected / exposed	16 / 90 (17.78%)		
occurrences (all)	19		
Neurotoxicity			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	6 / 90 (6.67%)		
occurrences (all)	6		
Paraesthesia oral			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Parkinson's disease			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Peripheral motor neuropathy			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Peripheral sensory neuropathy			
subjects affected / exposed	6 / 90 (6.67%)		
occurrences (all)	6		
Restless legs syndrome			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Syncope			
subjects affected / exposed	4 / 90 (4.44%)		
occurrences (all)	4		
Taste disorder			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences (all)	2		
Tremor			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 90 (10.00%)		
occurrences (all)	9		

Leukocytosis			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Leukopenia			
subjects affected / exposed	3 / 90 (3.33%)		
occurrences (all)	4		
Microcytosis			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Neutropenia			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Thrombocytopenia			
subjects affected / exposed	12 / 90 (13.33%)		
occurrences (all)	21		
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Vertigo			
subjects affected / exposed	5 / 90 (5.56%)		
occurrences (all)	9		
Eye disorders			
Binocular eye movement disorder			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Blepharitis			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Dry eye			
subjects affected / exposed	10 / 90 (11.11%)		
occurrences (all)	13		
Erythema of eyelid			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Eye disorder			

subjects affected / exposed	3 / 90 (3.33%)		
occurrences (all)	3		
Eye swelling			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Glaucoma			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Keratitis			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences (all)	2		
Lacrimation increased			
subjects affected / exposed	6 / 90 (6.67%)		
occurrences (all)	7		
Macular degeneration			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Scleral haemorrhage			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Vision blurred			
subjects affected / exposed	7 / 90 (7.78%)		
occurrences (all)	7		
Visual acuity reduced			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Visual field defect			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	6 / 90 (6.67%)		
occurrences (all)	7		
Abdominal pain			
subjects affected / exposed	5 / 90 (5.56%)		
occurrences (all)	7		

Abdominal pain lower			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences (all)	2		
Abdominal pain upper			
subjects affected / exposed	7 / 90 (7.78%)		
occurrences (all)	10		
Constipation			
subjects affected / exposed	32 / 90 (35.56%)		
occurrences (all)	70		
Diarrhoea			
subjects affected / exposed	20 / 90 (22.22%)		
occurrences (all)	38		
Dry mouth			
subjects affected / exposed	15 / 90 (16.67%)		
occurrences (all)	22		
Dyspepsia			
subjects affected / exposed	4 / 90 (4.44%)		
occurrences (all)	10		
Faeces discoloured			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Gastritis			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences (all)	2		
Gastrooesophageal			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Gingival bleeding			
subjects affected / exposed	5 / 90 (5.56%)		
occurrences (all)	9		
Gingival pain			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences (all)	4		
Glossitis			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		

Haematochezia			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Haemorrhoids			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Lip swelling			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Mouth haemorrhage			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Mouth ulceration			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	43 / 90 (47.78%)		
occurrences (all)	126		
Odynophagia			
subjects affected / exposed	3 / 90 (3.33%)		
occurrences (all)	3		
Peridontal disease			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	10 / 90 (11.11%)		
occurrences (all)	12		
Toothache			
subjects affected / exposed	4 / 90 (4.44%)		
occurrences (all)	4		
Vomiting			
subjects affected / exposed	20 / 90 (22.22%)		
occurrences (all)	33		

Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Cholestasis			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Hepatic function abnormal			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Hepatic pain			
subjects affected / exposed	4 / 90 (4.44%)		
occurrences (all)	4		
Hepatitis			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Hyperbilirubinaemia			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	14 / 90 (15.56%)		
occurrences (all)	14		
Dermatitis allergic			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Dermatitis contact			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences (all)	4		
Eczema			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Erythema			

subjects affected / exposed	4 / 90 (4.44%)		
occurrences (all)	5		
Hyperhidrosis			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Nail disorder			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences (all)	2		
Nail ridging			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences (all)	2		
Night sweats			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Onychoclasia			
subjects affected / exposed	4 / 90 (4.44%)		
occurrences (all)	5		
Pain of skin			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Petechiae			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Photosensitivity reaction			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Polymorphic light eruption			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	5 / 90 (5.56%)		
occurrences (all)	5		
Purpura			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Rash			

subjects affected / exposed	8 / 90 (8.89%)		
occurrences (all)	10		
Rash maculo-papular			
subjects affected / exposed	4 / 90 (4.44%)		
occurrences (all)	4		
Skin discolouration			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Skin disorder			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Skin fissures			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Skin irritation			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences (all)	2		
Skin lesion			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences (all)	3		
Spider naevus			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Umbilical erythema			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences (all)	2		
Haematuria			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Micturition incontinence			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		

Urinary incontinence subjects affected / exposed occurrences (all)	3 / 90 (3.33%) 4		
Urinary retention subjects affected / exposed occurrences (all)	1 / 90 (1.11%) 1		
Endocrine disorders Goitre subjects affected / exposed occurrences (all)	1 / 90 (1.11%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	20 / 90 (22.22%) 43		
Back pain subjects affected / exposed occurrences (all)	9 / 90 (10.00%) 18		
Bone pain subjects affected / exposed occurrences (all)	4 / 90 (4.44%) 4		
Bursitis subjects affected / exposed occurrences (all)	2 / 90 (2.22%) 2		
Muscle spasms subjects affected / exposed occurrences (all)	8 / 90 (8.89%) 14		
Muscular weakness subjects affected / exposed occurrences (all)	2 / 90 (2.22%) 2		
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	1 / 90 (1.11%) 1		
Musculoskeletal pain subjects affected / exposed occurrences (all)	2 / 90 (2.22%) 5		
Musculoskeletal stiffness			

subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	19 / 90 (21.11%)		
occurrences (all)	33		
Neck pain			
subjects affected / exposed	3 / 90 (3.33%)		
occurrences (all)	4		
Osteoarthritis			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Osteonecrosis			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	15 / 90 (16.67%)		
occurrences (all)	27		
Periarthritis			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	2		
Sacral pain			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Temporomandibular joint syndrome			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Tendonitis			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Infections and infestations			
Bronchitis			
subjects affected / exposed	4 / 90 (4.44%)		
occurrences (all)	5		
Candida infection			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		

Cellulitis			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	2		
Conjunctivitis			
subjects affected / exposed	5 / 90 (5.56%)		
occurrences (all)	7		
Cystitis			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences (all)	4		
Device related infection			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Escherichia urinary tract infection			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences (all)	2		
Fungal infection			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Furuncle			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	3 / 90 (3.33%)		
occurrences (all)	3		
Gastroenteritis viral			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Gingivitis			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Herpes zoster			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Infection			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences (all)	2		

Influenza			
subjects affected / exposed	10 / 90 (11.11%)		
occurrences (all)	12		
Localised infection			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	6 / 90 (6.67%)		
occurrences (all)	7		
Oral candidiasis			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Oral herpes			
subjects affected / exposed	4 / 90 (4.44%)		
occurrences (all)	4		
Otitis media			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Pharyngitis			
subjects affected / exposed	4 / 90 (4.44%)		
occurrences (all)	5		
Pneumonia			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences (all)	2		
Postoperative wound infection			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Respiratory tract infection			
subjects affected / exposed	6 / 90 (6.67%)		
occurrences (all)	8		
Rhinitis			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences (all)	7		
Rhinotracheitis			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		

Sinusitis			
subjects affected / exposed	9 / 90 (10.00%)		
occurrences (all)	14		
Skin infection			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Soft tissue infection			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Tonsillitis			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Tooth infection			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Tracheitis			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	12 / 90 (13.33%)		
occurrences (all)	14		
Urinary tract infection			
subjects affected / exposed	13 / 90 (14.44%)		
occurrences (all)	48		
Vaginal infection			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Viral infection			
subjects affected / exposed	3 / 90 (3.33%)		
occurrences (all)	3		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	22 / 90 (24.44%)		
occurrences (all)	33		
Diabetes mellitus			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Fluid retention			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Folate deficiency			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		
Hypercalcaemia			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences (all)	2		
Hyperglycaemia			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences (all)	2		
Hypocalcaemia			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences (all)	3		
Hypokaliaemia			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences (all)	3		
Hyponatraemia			
subjects affected / exposed	3 / 90 (3.33%)		
occurrences (all)	5		
Iron deficiency			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences (all)	2		
Vitamin D deficiency			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 June 2012	Belgium - New/updated protocol and ICF
02 August 2012	The Netherlands - New/updated protocol and ICF
12 November 2012	The Netherlands - New/updated protocol and ICF
15 November 2012	The Netherlands - Addition of sites
04 December 2012	Belgium - New/updated protocol and ICF, addition of sites
18 January 2014	The Netherlands - New/updated ICF
27 May 2014	The Netherlands - New/updated protocol and ICF
18 July 2014	Belgium - New/updated protocol and ICF
02 October 2014	The Netherlands - New/updated protocol and ICF
05 August 2015	Belgium - New/updated protocol and ICF
01 October 2015	Belgium - New/updated ICF (addendum)
23 December 2015	The Netherlands - New/updated protocol and ICF
06 April 2016	the Netherlands - Updated IB
24 May 2016	the Netherlands - RSI change
02 June 2016	Belgium - RSI change
23 March 2017	Belgium - Temp halt recr
03 April 2017	The Netherlands - Temp halt of recr
20 April 2017	Belgium - Change RSI
25 April 2017	The Netherlands - Change of RSI
13 July 2017	Belgium - New/updated protocol and ICF (addendum)
13 October 2017	The Netherlands - New/updated protocol and ICF (addendum)

06 July 2018	The Netherlands - Updated IB
06 December 2018	Belgium - New/updated ICF (addendum)
21 January 2019	The Netherlands - New/updated ICF (addendum)
02 May 2019	Belgium - RSI change
23 May 2019	The Netherlands - RSI change
21 January 2021	Belgium - RSI
12 April 2021	The Netherlands - New/updated protocol and ICF
21 October 2021	Belgium - Move of Bordet
09 March 2022	Belgium - New insurance certificate

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

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.
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Notes: