Clinical trial results:
A phase II study investigating preoperative MPDL3280A in operable transitional cell carcinoma of the bladder

Summary

EudraCT number	2015-001112-35
Trial protocol	GB ES DE FR NL
Global end of trial date	11 June 2020

Results information

Result version number	v1 (current)
This version publication date	23 June 2021
First version publication date	23 June 2021

Trial information

Trial identification

Sponsor protocol code	010463QM

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02662309
WHO universal trial number (UTN)	-
Other trial identifiers	Clinicaltrials.gov: NCT02662309

Notes:

Sponsors

Sponsor organisation name	Queen Mary University of London
Sponsor organisation address	Mile End Road, London, United Kingdom, E1 4NS
Public contact	ABACUS Trial Coordinator, Queen Mary University of London, +44 02078828497, bci-cecmmonitoring@qmul.ac.uk
Scientific contact	Prof Thomas Powles, Queen Mary University of London, +44 02078828497, bci-cecmmonitoring@qmul.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 May 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 June 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine MPDL3280A's (also known as atezolizumab) ability to reduce the size of bladder cancer before surgery (measured as pathological complete response rate), and assess the impact of the drug on the body's immune system.

Protection of trial subjects:

The study design aimed to minimise potential risks. Eligibility criteria were selected to enhance the safety of patients in this trial and a number of exclusion criteria were specifically based on the known safety profile of the study drug. Treatment with atezolizumab in the "window of opportunity" between enrolment and surgery did not delay participants' planned cystectomy surgeries. Participants were fully informed about the study prior to participation, including planned study procedures and the potential risks. Many of the procedures/ assessments carried out in the study are offered as standard-of-care, and participant safety was monitored at regular study visits. Relevant data protection and privacy regulations were followed throughout.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 February 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 7
Country: Number of subjects enrolled	Spain: 56
Country: Number of subjects enrolled	United Kingdom: 24
Country: Number of subjects enrolled	France: 9
Worldwide total number of subjects	96
EEA total number of subjects	72

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	17
From 65 to 84 years	77
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

From 29-Feb-2016, 118 patients were screened for the ABACUS trial. 96 patients were subsequently enrolled. Patients were recruited from multiple centres in the UK, Spain, France, and Netherlands. 1 patient was withdrawn prior to treatment as eligibility criteria were not met. 95 patients continued to receive treatment and are included in analyses.

Pre-assignment

Screening details:

Inclusion criteria included patients with histologically confirmed muscle-invasive bladder cancer (T2-4aN0M0) with a majority of urothelial component and residual disease after transurethral resection of the bladder tumour. Patients were either ineligible for or refused cisplatin-based neoadjuvant chemotherapy.

Period 1

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

Arms

Arm title	Atezolizumab Treatment (Full analysis set)

Arm description:

Patients receive 2x 3-weekly cycles of atezolizumab (one infusion on the first day of each cycle) prior to cystectomy surgery. This arm/population includes all patients who meet the eligibility criteria and have had at least 1 cycle of atezolizumab, regardless of whether they were later found to be ineligible or a protocol violator.

Arm type	Experimental
Investigational medicinal product name	atezolizumab
Investigational medicinal product code	
Other name	MPDL3280A
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

2 cycles of 1200 mg atezolizumab administered by IV infusion every 3 weeks.

Number of subjects in period 1[1]	Atezolizumab Treatment (Full analysis set)
Started	95
Received Cycle 1 of atezolizumab	95
Received Cycle 2 of atezolizumab	75
Underwent cystectomy	87
Completed	69
Not completed	26
Consent withdrawn by subject	2
Death	22
Lost to follow-up	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The worldwide number enrolled in the trial is 96 subjects. This includes 1 subject that was enrolled in error and not included in any analysis sets.

The 'Overall trial' / baseline period is effectively the safety set and full analysis set (FAS) population of 95 subjects. It does not include the 1 subject that was excluded from the study following enrolment.

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial
Reporting group description:	
Includes all patients who meet the eligibility criteria and received at least one administration of atezolizumab.	

Reporting group values	Overall trial	Total	
Number of subjects	95	95	
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)	17	17	
From 65-84 years	76	76	
85 years and over	2	2	
Age continuous Units: years			
median	73		
inter-quartile range (Q1-Q3)	53 to 87	-	
Gender categorical Units: Subjects			
Female	14	14	
Male	81	81	
Race Units: Subjects			
Asian (Bangladeshi)	1	1	
Black (African)	1	1	
Other	1	1	
White	89	89	
Not specified	3	3	
Tumour grade Units: Subjects			
Grade 1	1	1	
Grade 2	9	9	
Grade 3	75	75	
Grade 4	9	9	
N/A	1	1	
Tumour stage (Pathological) Units: Subjects			
T2a (invades superficial muscle propria)	39	39	
T2b (invades deep muscle propria)	31	31	

T3a (invades perivesical tissue microscopically)	9	9	
T3b (invades perivesical tissue macroscopically)	8	8	
T4a (invades prostate, uterus, vagina)	8	8	
Lymph node stage			
Units: Subjects			
N0 (No lymph node metastasis)	95	95	
Metastatic stage			
Units: Subjects			
M0 (No distant metastasis)	95	95	
Has the patient had previous NMIBC?			
NMIBC = Non-Muscle Invasive Bladder Cancer			
Units: Subjects			
Yes	14	14	
No	81	81	
Stage of previous NMIBC			
Units: Subjects			
Tis	1	1	
Ta	5	5	
T1	8	8	
Not applicable	81	81	
Previous NMIBC: CIS			
Units: Subjects			
Yes	5	5	
No	9	9	
Not applicable	81	81	
PD-L1 status			
PD-L1 positive is defined as all patients with a value greater than or equal to 5 for PD-L1 at the pre-treatment visit. PD-L1 negative is defined as all patients with a value less than 5 for PD-L1 at the pre-treatment visit. PD-L1 status unknown is defined as all patients without PD-L1 data at the pre-treatment visit.			
Units: Subjects			
PD-L1 positive	39	39	
PD-L1 negative	51	51	
PD-L1 status unknown	5	5	
CD8-GZMB status			
CD8-GZMB high (low) are defined as all patients with a value greater than (less than or equal to) the median for that measurement at the pre-treatment visit. CD8-GZMB status of unknown is defined as all patients without data at the pre-treatment visit for that measurement.			
Units: Subjects			
CD8-GZMB high	36	36	
CD8-GZMB low	35	35	
CD8-GZMB status unknown	24	24	
TMB status			
TMB high (low) are defined as all patients with a value greater than (less than or equal to) the median for that measurement at the pre-treatment visit. TMB status of unknown is defined as all patients without data at the pre-treatment visit for that measurement.			
Units: Subjects			
TMB high	39	39	
TMB low	42	42	
TMB status unknown	14	14	

Radiological measurable disease			
Measurable disease at baseline is a tumour diameter of >10mm.			
Units: Subjects			
Yes	69	69	
No	20	20	
Unknown	6	6	
Received BCG vaccination Units: Subjects			
Yes	11	11	
No	84	84	
Smoking status Units: Subjects			
Never at any time been a regular smoker	21	21	
Ex-smoker (smoked regularly in the past)	53	53	
Current smoker (either regular or occasional)	21	21	
ECOG Performance Status			
ECOG = Eastern Cooperative Oncology Group			
Units: Subjects			
ECOG Grade 0	71	71	
ECOG Grade 1	24	24	
Pathological tumour size Units: millimeter(s)			
median	25		
inter-quartile range (Q1-Q3)	0 to 80	-	
Intertumoral CD8 count			
N=89 for this baseline characteristic, due to the remainder of patients having missing CD8 count data at baseline.			
Units: CD8			
median	186.3		
inter-quartile range (Q1-Q3)	69.8 to 396.2	-	

End points

End points reporting groups

Reporting group title	Atezolizumab Treatment (Full analysis set)

Reporting group description:

Patients receive 2x 3-weekly cycles of atezolizumab (one infusion on the first day of each cycle) prior to cystectomy surgery. This arm/population includes all patients who meet the eligibility criteria and have had at least 1 cycle of atezolizumab, regardless of whether they were later found to be ineligible or a protocol violator.

Primary: Efficacy of atezolizumab pre-cystectomy with respect to pathological complete response rate (pCRR)

End point title	Efficacy of atezolizumab pre-cystectomy with respect to pathological complete response rate (pCRR)[1]

End point description:

Pathological complete response (pCR) is defined as no microscopic evidence of residual disease in the bladder based on histological evaluation of the resected bladder specimen collected during cystectomy (pT0/Tis/Cis).
Pathological complete response rate (pCRR) is defined as the number of patients with a pCR divided by the number of patients analysed.

End point type	Primary

End point timeframe:

2-3 months (timeframe dependent on delay to surgery)

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: ABACUS was a single arm study with no comparison groups, therefore statistical analysis section not relevant.

End point values	Atezolizumab Treatment (Full analysis set)			
Subject group type	Reporting group			
Number of subjects analysed	88[2]			
Units: Patients				
Patients with pathological complete response (pCR)	27			
Patients with major pathological response (MPR)	7			

Notes:

[2] - 88 patients were eligible for pCR/MPR analysis.

Statistical analyses

No statistical analyses for this end point

Primary: Effect of atezolizumab pre-cystectomy with respect to dynamic changes in T-cell levels

End point title	Effect of atezolizumab pre-cystectomy with respect to dynamic changes in T-cell levels[3]

End point description:

T cell sub-populations in tumour samples collected from patients receiving at least 1 cycle of treatment.

Pre-treatment is tumour samples taken before the start of Atezolizumab (biopsy) and post-treatment is samples taken at the end of Atezolizumab (excision/biopsy).

End point type	Primary

End point timeframe:

2-3 months (timeframe dependent on delay to surgery)

Notes:

[3] - 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: ABACUS was a single arm study with no comparison groups, therefore statistical analysis section not relevant.

End point values	Atezolizumab Treatment (Full analysis set)			
Subject group type	Reporting group			
Number of subjects analysed	54[4]			
Units: CD8				
median (inter-quartile range (Q1-Q3))				
Pre-treatment CD8	111.9 (48.9 to 291.4)			
Post-treatment CD8	198.8 (69.4 to 558.1)			

Notes:

[4] - Patients with pre and post-treatment CD8 result.

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy of atezolizumab pre-cystectomy with respect to anti-tumour effects as measured by radiological response (RR)

End point title	Efficacy of atezolizumab pre-cystectomy with respect to anti-tumour effects as measured by radiological response (RR)

End point description:

CT or MRI scan taken at screening and pre-cystectomy visits. RR is defined as a ≥30% decrease in tumour diameter from the baseline scan.

End point type	Secondary

End point timeframe:

Approx 34 weeks (timeframe dependent on delay to pre-cystectomy visit)

End point values	Atezolizumab Treatment (Full analysis set)			
Subject group type	Reporting group			
Number of subjects analysed	58[5]			
Units: Patients with radiological response (RR)	13			

Notes:

[5] - Patients eligible for radiological response rate analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy of atezolizumab pre-cystectomy with respect to anti-tumour effects based on disease free survival (DFS)

End point title	Efficacy of atezolizumab pre-cystectomy with respect to anti-tumour effects based on disease free survival (DFS)

End point description:

Disease and survival data is reviewed at post-surgery visits and at 1 and 2 years post-cystectomy. Disease recurrence is defined as the first evidence of relapse (based on local investigator assessments) or death from any cause.

End point type	Secondary

End point timeframe:

Up to 2 years post-cystectomy

End point values	Atezolizumab Treatment (Full analysis set)			
Subject group type	Reporting group			
Number of subjects analysed	95[6]			
Units: Percentage				
DFS rate at 12 months	73			
DFS rate at 24 months	68			

Notes:

[6] - Median DFS was Not Reached.

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy of atezolizumab pre-cystectomy with respect to anti-tumour effects based on overall survival (OS)

End point title	Efficacy of atezolizumab pre-cystectomy with respect to anti-tumour effects based on overall survival (OS)

End point description:

Disease and survival data is reviewed at post-surgery visits and at 1 and 2 years post-cystectomy.

End point type	Secondary

End point timeframe:

Up to 2 years post-cystectomy

End point values	Atezolizumab Treatment (Full analysis set)			
Subject group type	Reporting group			
Number of subjects analysed	95[7]			
Units: Percentage				
OS rate at 12 months	84			
OS rate at 24 months	77			

Notes:
[7] - Median OS was Not Reached.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from informed consent up to 4 weeks post-cystectomy.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	Safety Set population

Reporting group description:

Safety Set population is defined as all patients enrolled into the trial who received at least one administration of study treatment.

Serious adverse events	Safety Set population		
Total subjects affected by serious adverse events			
subjects affected / exposed	32 / 95 (33.68%)		
number of deaths (all causes)	22		
number of deaths resulting from adverse events			
Investigations			
Transaminases increased			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Wound dehiscence			
subjects affected / exposed	2 / 95 (2.11%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac arrest			

subjects affected / exposed	1 / 95 (1.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiogenic shock			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Coronary artery disease			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocarditis			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 95 (4.21%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza like illness			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 95 (2.11%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Pulmonary embolism			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Chronic kidney disease			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract obstruction			

subjects affected / exposed	1 / 95 (1.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	12 / 95 (12.63%)		
occurrences causally related to treatment / all	0 / 13		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	3 / 95 (3.16%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Abdominal infection			
subjects affected / exposed	2 / 95 (2.11%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac infection			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 95 (1.05%)		
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 / 95 (1.05%)		
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	Safety Set population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	87 / 95 (91.58%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	8 / 95 (8.42%)		
occurrences (all)	8		
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 95 (5.26%)		
occurrences (all)	6		
Hypotension			
subjects affected / exposed	4 / 95 (4.21%)		
occurrences (all)	4		
Hot flush			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences (all)	1		
Lymphorrhoea			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	39 / 95 (41.05%)		
occurrences (all)	50		
Pyrexia			
subjects affected / exposed	10 / 95 (10.53%)		
occurrences (all)	10		
Pain			
subjects affected / exposed	6 / 95 (6.32%)		
occurrences (all)	8		

Oedema subjects affected / exposed occurrences (all) Influenza like illness subjects affected / exposed occurrences (all) Chills subjects affected / exposed occurrences (all) Mucosal inflammation subjects affected / exposed occurrences (all)	5 / 95 (5.26%) 6 3 / 95 (3.16%) 3 2 / 95 (2.11%) 3 2 / 95 (2.11%) 2		
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	2 / 95 (2.11%) 2		
Reproductive system and breast disorders Pelvic haematoma subjects affected / exposed occurrences (all)	1 / 95 (1.05%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Respiratory failure subjects affected / exposed occurrences (all) Pleural effusion subjects affected / exposed occurrences (all) Bronchial obstruction subjects affected / exposed occurrences (all)	8 / 95 (8.42%) 8 5 / 95 (5.26%) 7 4 / 95 (4.21%) 4 2 / 95 (2.11%) 2 1 / 95 (1.05%) 1		

Catarrh subjects affected / exposed occurrences (all)	1 / 95 (1.05%) 1		
Dysphonia subjects affected / exposed occurrences (all)	1 / 95 (1.05%) 1		
Sneezing subjects affected / exposed occurrences (all)	1 / 95 (1.05%) 1		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	3 / 95 (3.16%) 3		
Confusional state subjects affected / exposed occurrences (all)	2 / 95 (2.11%) 2		
Insomnia subjects affected / exposed occurrences (all)	1 / 95 (1.05%) 1		
Agitation subjects affected / exposed occurrences (all)	1 / 95 (1.05%) 1		
Investigations Blood creatinine increased subjects affected / exposed occurrences (all)	9 / 95 (9.47%) 12		
Transaminases increased subjects affected / exposed occurrences (all)	7 / 95 (7.37%) 18		
Weight decreased subjects affected / exposed occurrences (all)	5 / 95 (5.26%) 7		
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	2 / 95 (2.11%) 2		
Blood creatine phosphokinase increased			

subjects affected / exposed	1 / 95 (1.05%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences (all)	1		
Neutrophil count decreased			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences (all)	1		
Lymphocyte count increased			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences (all)	1		
Nutritional condition abnormal			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences (all)	1		
Platelet count increased			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Wound dehiscence			
subjects affected / exposed	3 / 95 (3.16%)		
occurrences (all)	3		
Urostomy complication			
subjects affected / exposed	2 / 95 (2.11%)		
occurrences (all)	2		
Gastroparesis postoperative			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences (all)	1		
Infusion related reaction			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences (all)	1		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	3 / 95 (3.16%)		
occurrences (all)	3		
Atrial flutter			

subjects affected / exposed	2 / 95 (2.11%)		
occurrences (all)	2		
Coronary artery disease			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences (all)	1		
Myocardial infarction			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences (all)	1		
Palpitations			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 95 (3.16%)		
occurrences (all)	3		
Taste disorder			
subjects affected / exposed	2 / 95 (2.11%)		
occurrences (all)	2		
Cognitive disorder			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences (all)	1		
Neuromyopathy			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences (all)	1		
Frontotemporal dementia			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	19 / 95 (20.00%)		
occurrences (all)	40		
Leukocytosis			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences (all)	1		
Thrombocytopenia			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences (all)	2		
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences (all)	1		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	16 / 95 (16.84%)		
occurrences (all)	21		
Diarrhoea			
subjects affected / exposed	11 / 95 (11.58%)		
occurrences (all)	13		
Ileus			
subjects affected / exposed	9 / 95 (9.47%)		
occurrences (all)	9		
Abdominal pain			
subjects affected / exposed	6 / 95 (6.32%)		
occurrences (all)	7		
Vomiting			
subjects affected / exposed	4 / 95 (4.21%)		
occurrences (all)	4		
Nausea			
subjects affected / exposed	4 / 95 (4.21%)		
occurrences (all)	4		
Dry mouth			
subjects affected / exposed	3 / 95 (3.16%)		
occurrences (all)	3		
Abdominal distension			

subjects affected / exposed	2 / 95 (2.11%)		
occurrences (all)	2		
Dyspepsia			
subjects affected / exposed	2 / 95 (2.11%)		
occurrences (all)	2		
Fistula of small intestine			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences (all)	1		
Hernial eventration			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences (all)	1		
Glossodynia			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences (all)	1		
Ascites			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences (all)	1		
Buccal mucosal roughening			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences (all)	1		
Flatulence			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences (all)	1		
Haemorrhoids			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	11 / 95 (11.58%)		
occurrences (all)	12		
Rash			
subjects affected / exposed	9 / 95 (9.47%)		
occurrences (all)	9		
Cold sweat			
subjects affected / exposed	2 / 95 (2.11%)		
occurrences (all)	2		

Dry skin			
subjects affected / exposed	2 / 95 (2.11%)		
occurrences (all)	2		
Decubitus ulcer			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences (all)	2		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	9 / 95 (9.47%)		
occurrences (all)	10		
Dysuria			
subjects affected / exposed	6 / 95 (6.32%)		
occurrences (all)	6		
Acute kidney injury			
subjects affected / exposed	3 / 95 (3.16%)		
occurrences (all)	3		
Nocturia			
subjects affected / exposed	3 / 95 (3.16%)		
occurrences (all)	3		
Urinary incontinence			
subjects affected / exposed	3 / 95 (3.16%)		
occurrences (all)	3		
Chronic kidney disease			
subjects affected / exposed	2 / 95 (2.11%)		
occurrences (all)	2		
Proteinuria			
subjects affected / exposed	2 / 95 (2.11%)		
occurrences (all)	3		
Urinary tract obstruction			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences (all)	1		
Glycosuria			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences (all)	1		
Oliguria			

subjects affected / exposed occurrences (all) Leukocyturia subjects affected / exposed occurrences (all) Pollakiuria subjects affected / exposed occurrences (all) Renal impairment subjects affected / exposed occurrences (all)	1 / 95 (1.05%) 1 1 / 95 (1.05%) 1 1 / 95 (1.05%) 1 1 / 95 (1.05%) 1		
Endocrine disorders Adrenal insufficiency subjects affected / exposed occurrences (all) Hypothyroidism subjects affected / exposed occurrences (all) Hyperparathyroidism subjects affected / exposed occurrences (all)	 1 / 95 (1.05%) 1 1 / 95 (1.05%) 1 1 / 95 (1.05%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all) Ligament sprain subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all)	 4 / 95 (4.21%) 5 3 / 95 (3.16%) 5 1 / 95 (1.05%) 1 1 / 95 (1.05%) 1		
Infections and infestations			

Urinary tract infection subjects affected / exposed occurrences (all)	20 / 95 (21.05%) 24		
Respiratory tract infection subjects affected / exposed occurrences (all)	9 / 95 (9.47%) 11		
Abdominal infection subjects affected / exposed occurrences (all)	4 / 95 (4.21%) 4		
Wound infection subjects affected / exposed occurrences (all)	4 / 95 (4.21%) 4		
Fungal infection subjects affected / exposed occurrences (all)	2 / 95 (2.11%) 2		
Infection subjects affected / exposed occurrences (all)	2 / 95 (2.11%) 2		
Bacterial infection subjects affected / exposed occurrences (all)	2 / 95 (2.11%) 3		
Sepsis subjects affected / exposed occurrences (all)	1 / 95 (1.05%) 1		
Viral skin infection subjects affected / exposed occurrences (all)	1 / 95 (1.05%) 1		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	16 / 95 (16.84%) 22		
Hypophosphataemia subjects affected / exposed occurrences (all)	5 / 95 (5.26%) 7		
Hyperkalaemia			

subjects affected / exposed	3 / 95 (3.16%)		
occurrences (all)	3		
Hypokalaemia			
subjects affected / exposed	2 / 95 (2.11%)		
occurrences (all)	2		
Hyperglycaemia			
subjects affected / exposed	2 / 95 (2.11%)		
occurrences (all)	2		
Hyperamylasaemia			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences (all)	1		
Hypermagnesaemia			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences (all)	1		
Hypernatraemia			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences (all)	1		
Hyperproteinaemia			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences (all)	1		
Hypocalcaemia			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences (all)	1		
Hypomagnesaemia			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 September 2018	Change of sponsor representative and statistician. Clarification of trial endpoints. Safety update and updated Investigator's Brochure.
01 October 2018	Further clarification of primary trial endpoints.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31686036

http://www.ncbi.nlm.nih.gov/pubmed/33612455