Clinical trial results:
A randomized, double-blind, multicenter study to assess the efficacy and safety of a 6 months oral treatment with the chymase inhibitor BAY1142524 at a dose of 25 mg BID in comparison to placebo on top of standard of care in patients with type II diabetes and a clinical diagnosis of diabetic kidney disease

Summary

EudraCT number	2017-000656-26
Trial protocol	SE FI DK ES BG IT
Global end of trial date	10 October 2019

Results information

Result version number	v1 (current)
This version publication date	27 September 2020
First version publication date	27 September 2020

Trial information

Trial identification

Sponsor protocol code	BAY1142524/18933

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03412006
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser Wilhelm Allee, Leverkusen, Germany, 51368
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com

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 October 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the change in urinary albumin-to-creatinine ratio (UACR) from baseline values obtained at Visit 1 to 6 months after treatment with fulacimstat (BAY1142524), in comparison to placebo, on top of standard of care therapy

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy:

Background treatment for diabetic kidney disease comprised the treatment with an angiotensin receptor blocker (ARB) or an angiotensin-converting enzyme inhibitor (ACEI) at the maximum tolerated dose since at least 3 months prior to the screening visit whereby the maximum tolerated dose had to be at least as high as the minimal recommended target dose of an ACEI or ARB according to international or local guidelines.

Evidence for comparator:

No

Actual start date of recruitment	02 February 2018
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	Bulgaria: 32
Country: Number of subjects enrolled	Denmark: 11
Country: Number of subjects enrolled	Finland: 26
Country: Number of subjects enrolled	Israel: 41
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Spain: 19
Country: Number of subjects enrolled	Sweden: 13
Worldwide total number of subjects	147
EEA total number of subjects	106

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)	36
From 65 to 84 years	111
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First patient first visit of the study was on 02-Feb-2018 and last patient last visit on 10-Oct-2019.

Pre-assignment

Screening details:

361 subjects were screened of whom 214 patients were screening failures.147 patients were randomized and treated. 139 patients completed the treatment phase, of whom 1 patient did not complete the follow-up. In total, 144 patients completed the follow-up.

Period 1

Period 1 title	Study period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Carer, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Fulacimstat

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Fulacimstat
Investigational medicinal product code	BAY1142524
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

25 mg twice (BID) for 24 weeks

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo matching Fulacimstat 25 mg tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

For 24 weeks

Number of subjects in period 1	Fulacimstat	Placebo
Started	99	48
Completed	94	45
Not completed	5	3
Adverse event, non-fatal	3	2
Non-compliance to study drug	1	-

Failure to meet continuation criteria	-	1
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Fulacimstat
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Fulacimstat	Placebo	Total
Number of subjects	99	48	147
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	20	16	36
From 65-84 years	79	32	111
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	69.1	66.5	
standard deviation	± 6.3	± 7.8	-
Gender Categorical Units: Subjects			
Female	15	8	23
Male	84	40	124
Albuminuria at Visit 1 Units: Subjects			
Microalbuminuria	78	32	110
Macroalbuminuria	21	16	37
Body mass index (BMI) Units: kg/m2			
arithmetic mean	31.38	31.18	
standard deviation	± 4.89	± 4.68	-
Urinary albumin-to-creatinine ratio (UACR) at Visit 1 Units: mg/g			
median	140.80	129.85	
full range (min-max)	31.56 to 2429	29.59 to 2156	-
Estimated glomerular filtration rate (eGFR) at Visit 1 Units: mL/min/1.73 m2			
arithmetic mean	60.5	61.2	
standard deviation	± 17.1	± 16.5	-

Subject analysis sets	
Subject analysis set title	Safety Analysis Set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety analysis set included all enrolled patients who received at least 1 dose of study medication.	
Subject analysis set title	Per protocol set (PPS)
Subject analysis set type	Per protocol
Subject analysis set description:	
The PPS included all enrolled patients who completed the treatment period according to protocol.	

Reporting group values	Safety Analysis Set (SAF)	Per protocol set (PPS)	
Number of subjects	147	121	
Age Categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	36		
From 65-84 years	111		
85 years and over	0		
Age Continuous			
Units: years			
arithmetic mean	68.2	68.2	
standard deviation	± 6.9	± 7.0	
Gender Categorical			
Units: Subjects			
Female	23	19	
Male	124	102	
Albuminuria at Visit 1			
Units: Subjects			
Microalbuminuria	110	90	
Macroalbuminuria	37	31	
Body mass index (BMI)			
Units: kg/m2			
arithmetic mean	31.31	31.14	
standard deviation	± 4.81	± 4.84	
Urinary albumin-to-creatinine ratio (UACR) at Visit 1			
Units: mg/g			
median	131.69	131.69	
full range (min-max)	29.59 to 2429	31.56 to 2429	
Estimated glomerular filtration rate (eGFR) at Visit 1			
Units: mL/min/1.73 m2			
arithmetic mean	60.77	60.11	
standard deviation	± 16.90	± 16.13	

End points

End points reporting groups

Reporting group title	Fulacimstat
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Safety Analysis Set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety analysis set included all enrolled patients who received at least 1 dose of study medication.	
Subject analysis set title	Per protocol set (PPS)
Subject analysis set type	Per protocol
Subject analysis set description:	
The PPS included all enrolled patients who completed the treatment period according to protocol.	

Primary: Change in urinary albumin to creatinine ratio (UACR) for total population

End point title	Change in urinary albumin to creatinine ratio (UACR) for total population
End point description:	
The change in urinary albumin to creatinine ratio (UACR) between baseline and 6 months after treatment with fulacimstat, in comparison to placebo, on top of standard of care therapy, for patients with either microalbumanuria or macroalbumnuria (total population; PPS).	
End point type	Primary
End point timeframe:	
Baseline and at 6 months	

End point values	Fulacimstat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	38		
Units: None				
geometric mean (standard deviation)				
UACR (for PPS)	1.030 (± 2.146)	1.274 (± 2.105)		

Statistical analyses

Statistical analysis title	Treatment effect (Total population; PPS)
Statistical analysis description:	
Fulacimstat/Placebo for PPS	
Comparison groups	Fulacimstat v Placebo

Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1477
Method	ANCOVA
Parameter estimate	LS mean ratio (fulacimstat/placebo)
Point estimate	0.804
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.627
upper limit	1.03

Secondary: Number of subjects with treatment-emergent adverse events (TEAEs)

End point title	Number of subjects with treatment-emergent adverse events (TEAEs)
End point description:	
Number of subjects with treatment-emergent adverse events (TEAEs)	
End point type	Secondary
End point timeframe:	
From first intake of study drug up to 3 days after last administration of study drug	

End point values	Fulacimstat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	48		
Units: Subjects				
Any TEAE	64	28		
TEAEs with intensity = Mild	38	15		
TEAEs with intensity = Moderate	22	13		
TEAEs with intensity = Severe	4	0		
Drug-related TEAEs	12	2		
Drug-related TEAEs with intensity = Mild	8	2		
Drug-related TEAEs with intensity = Moderate	4	0		
TEAEs related to protocol procedures	0	0		
TEAEs leading to drug discontinuation	3	1		
Any serious TEAE (TESAEs)	5	5		
Study drug-related TESAEs	0	0		
TESAEs related to protocol procedures	0	0		
TESAEs leading to drug discontinuation	1	1		
TEAEs with outcome death	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first administration of drug up to 3 days after last administration of drug	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups	
Reporting group title	Fulacimstat
Reporting group description:	
All enrolled patients who received at least 1 dose of fulacimstat	
Reporting group title	Placebo
Reporting group description:	
All enrolled patients who received at least 1 dose of placebo	

Serious adverse events	Fulacimstat	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 99 (5.05%)	5 / 48 (10.42%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 99 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 99 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Hernia repair			
subjects affected / exposed	0 / 99 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			

subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 99 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 99 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Ureteric obstruction			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Erysipelas			

subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Fulacimstat	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	64 / 99 (64.65%)	27 / 48 (56.25%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prolactin-producing pituitary tumour			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 99 (2.02%)	1 / 48 (2.08%)	
occurrences (all)	2	1	
Hypotension			
subjects affected / exposed	0 / 99 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Peripheral venous disease			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Cataract operation			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	4 / 99 (4.04%)	0 / 48 (0.00%)	
occurrences (all)	4	0	
Oedema peripheral			

subjects affected / exposed	2 / 99 (2.02%)	1 / 48 (2.08%)	
occurrences (all)	2	1	
Pyrexia			
subjects affected / exposed	1 / 99 (1.01%)	2 / 48 (4.17%)	
occurrences (all)	1	2	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 99 (1.01%)	1 / 48 (2.08%)	
occurrences (all)	1	1	
Dyspnoea exertional			
subjects affected / exposed	0 / 99 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Haemoptysis			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Lung hypoinflation			
subjects affected / exposed	0 / 99 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Psychiatric disorders			
Alcoholism			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Depression			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Product issues			
Device failure			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Investigations			
Amylase increased			
subjects affected / exposed	1 / 99 (1.01%)	1 / 48 (2.08%)	
occurrences (all)	1	1	
Blood creatinine increased			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	

Blood glucose increased			
subjects affected / exposed	0 / 99 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Blood potassium increased			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Blood pressure increased			
subjects affected / exposed	2 / 99 (2.02%)	2 / 48 (4.17%)	
occurrences (all)	2	2	
Cardiac murmur			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 99 (2.02%)	0 / 48 (0.00%)	
occurrences (all)	2	0	
Glomerular filtration rate decreased			
subjects affected / exposed	0 / 99 (0.00%)	2 / 48 (4.17%)	
occurrences (all)	0	2	
International normalised ratio decreased			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
International normalised ratio increased			
subjects affected / exposed	3 / 99 (3.03%)	0 / 48 (0.00%)	
occurrences (all)	3	0	
Lipase increased			
subjects affected / exposed	1 / 99 (1.01%)	2 / 48 (4.17%)	
occurrences (all)	1	2	
Prostatic specific antigen increased			
subjects affected / exposed	0 / 99 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Weight increased			
subjects affected / exposed	0 / 99 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			

Facial bones fracture			
subjects affected / exposed	0 / 99 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Road traffic accident			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Limb injury			
subjects affected / exposed	2 / 99 (2.02%)	0 / 48 (0.00%)	
occurrences (all)	2	0	
Upper limb fracture			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Post-traumatic pain			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Congenital, familial and genetic disorders			
Porphyria			
subjects affected / exposed	0 / 99 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Vitello-intestinal duct remnant			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 99 (1.01%)	1 / 48 (2.08%)	
occurrences (all)	1	1	
Atrioventricular block first degree			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Atrioventricular block second degree			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Coronary artery disease			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Extrasystoles			

subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Mitral valve incompetence			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Sinus tachycardia			
subjects affected / exposed	0 / 99 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Supraventricular extrasystoles			
subjects affected / exposed	1 / 99 (1.01%)	1 / 48 (2.08%)	
occurrences (all)	1	1	
Tachycardia			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Diastolic dysfunction			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 99 (1.01%)	1 / 48 (2.08%)	
occurrences (all)	1	2	
Headache			
subjects affected / exposed	4 / 99 (4.04%)	0 / 48 (0.00%)	
occurrences (all)	4	0	
Sciatica			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Tremor			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Cognitive disorder			
subjects affected / exposed	0 / 99 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Restless legs syndrome			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	

Orthostatic intolerance			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 99 (3.03%)	1 / 48 (2.08%)	
occurrences (all)	3	1	
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 99 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 99 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Conjunctival haemorrhage			
subjects affected / exposed	2 / 99 (2.02%)	0 / 48 (0.00%)	
occurrences (all)	2	0	
Diabetic retinopathy			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Abdominal pain			
subjects affected / exposed	1 / 99 (1.01%)	2 / 48 (4.17%)	
occurrences (all)	2	2	
Abdominal pain lower			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	4 / 99 (4.04%)	3 / 48 (6.25%)	
occurrences (all)	4	3	
Diarrhoea			
subjects affected / exposed	3 / 99 (3.03%)	1 / 48 (2.08%)	
occurrences (all)	4	1	

Dry mouth			
subjects affected / exposed	2 / 99 (2.02%)	0 / 48 (0.00%)	
occurrences (all)	2	0	
Dyspepsia			
subjects affected / exposed	0 / 99 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Flatulence			
subjects affected / exposed	1 / 99 (1.01%)	2 / 48 (4.17%)	
occurrences (all)	1	2	
Hiatus hernia			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Inguinal hernia			
subjects affected / exposed	0 / 99 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	0 / 99 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Eczema			
subjects affected / exposed	0 / 99 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	2	
Petechiae			
subjects affected / exposed	0 / 99 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Skin ulcer			

subjects affected / exposed	2 / 99 (2.02%)	0 / 48 (0.00%)	
occurrences (all)	2	0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Pollakiuria			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Polyuria			
subjects affected / exposed	2 / 99 (2.02%)	1 / 48 (2.08%)	
occurrences (all)	2	1	
Renal failure			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Urinary incontinence			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Renal impairment			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Ureterolithiasis			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 99 (2.02%)	2 / 48 (4.17%)	
occurrences (all)	2	2	
Back pain			
subjects affected / exposed	5 / 99 (5.05%)	0 / 48 (0.00%)	
occurrences (all)	5	0	
Muscle spasms			

subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal pain			
subjects affected / exposed	3 / 99 (3.03%)	0 / 48 (0.00%)	
occurrences (all)	3	0	
Myalgia			
subjects affected / exposed	1 / 99 (1.01%)	1 / 48 (2.08%)	
occurrences (all)	1	1	
Neck pain			
subjects affected / exposed	0 / 99 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	1 / 99 (1.01%)	2 / 48 (4.17%)	
occurrences (all)	1	2	
Tendonitis			
subjects affected / exposed	0 / 99 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Rheumatic disorder			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Clostridium difficile colitis			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Conjunctivitis			
subjects affected / exposed	2 / 99 (2.02%)	0 / 48 (0.00%)	
occurrences (all)	2	0	
Ear infection			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Erysipelas			
subjects affected / exposed	3 / 99 (3.03%)	0 / 48 (0.00%)	
occurrences (all)	3	0	
Gastroenteritis			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	

Hordeolum			
subjects affected / exposed	0 / 99 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	4 / 99 (4.04%)	5 / 48 (10.42%)	
occurrences (all)	7	5	
Sialoadenitis			
subjects affected / exposed	0 / 99 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Tonsillitis			
subjects affected / exposed	0 / 99 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	4 / 99 (4.04%)	0 / 48 (0.00%)	
occurrences (all)	4	0	
Urinary tract infection			
subjects affected / exposed	5 / 99 (5.05%)	1 / 48 (2.08%)	
occurrences (all)	6	1	
Soft tissue infection			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 99 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Hyperglycaemia			
subjects affected / exposed	3 / 99 (3.03%)	1 / 48 (2.08%)	
occurrences (all)	3	1	
Hyperkalaemia			
subjects affected / exposed	2 / 99 (2.02%)	0 / 48 (0.00%)	
occurrences (all)	2	0	
Hyperuricaemia			

subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Hypoglycaemia			
subjects affected / exposed	4 / 99 (4.04%)	3 / 48 (6.25%)	
occurrences (all)	5	6	
Hypokalaemia			
subjects affected / exposed	0 / 99 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Iron deficiency			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Vitamin B12 deficiency			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Vitamin B complex deficiency			
subjects affected / exposed	1 / 99 (1.01%)	0 / 48 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 May 2018	Amendment 01 (CSP v2.0) introduced changes regarding the inclusion of patients (ARB/ACEI medications, blood pressure and glycated hemoglobin [HbA1c] values), expected enrollment number, withdrawal of patients and handling of clinically relevant changes in safety parameters.

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.

None

Notes: