Clinical trial results:
Parallel-Group, Placebo-Controlled Randomized Study Investigating the Effect of Intravenous Iso-osmolar Iodinated Contrast Material Iodixanol (Visipaque™ Injection 320 mgI/mL) on Renal Function in Adults with Chronic Kidney Disease (CKD) Stage III or Stage IV Who Have Undergone Endovascular Aneurysm Repair (EVAR)

Summary

EudraCT number	2016-001668-13
Trial protocol	ES GB BE HU PL NL
Global end of trial date	19 October 2018

Results information

Result version number	v1 (current)
This version publication date	02 November 2019
First version publication date	02 November 2019

Trial information

Trial identification

Sponsor protocol code	GE-012-106

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03119662
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GE Healthcare Ltd.
Sponsor organisation address	The Grove Centre, White Lion Road, Amersham, Buckinghamshire, United Kingdom, HP7 9LL
Public contact	Medical Director - Nuclear Medicine, GE Healthcare Ltd., info@ge.com
Scientific contact	Medical Director - Nuclear Medicine, GE Healthcare Ltd., info@ge.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	07 December 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 October 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the safety of intravenous (i.v.) iodinated iso-osmolar iodixanol (Visipaque™ Injection 320 mgI/mL) usage in contrast-enhanced computed tomography (CECT) for CKD stage III/IV patients by evaluating the incidence of acute kidney injury (AKI) stage >=1, per acute kidney injury network (AKIN) serum creatinine (SCr) criteria [AKIN 2015] [Mehta et al. 2007], in patients undergoing CECT with iodixanol vs subjects receiving placebo and undergoing nonenhanced computed tomography (NECT) and an additional non–contrast-enhanced ultrasound imaging modality.

Protection of trial subjects:

A Steering Committee oversaw the study from conceptual protocol development, throughout study conduct and termination. In addition to the Steering Committee, a Critical Event Adjudication Committee (CEAC) was established to review all morbidity and mortality events (i.e., critical events, including Endovascular Aneurysm Repair (EVAR)-related post-baseline events). A Data Safety Monitoring Board (DSMB) was established to periodically review acute kidney injury (AKI) rates and make recommendations on the continuation of the study or potential requirement to amend the protocol. The Steering Committee and CEAC were not provided access to any treatment allocation information during the conduct of the study.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	08 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	Spain: 2
Country: Number of subjects enrolled	United States: 2
Worldwide total number of subjects	4
EEA total number of subjects	2

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)	0
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The Study was conducted at 29 sites in United States of America & Europe from 8 February 2018 to 19 October 2018. A total of 8 subjects with Chronic Kidney Disease (CKD) stage III/IV were enrolled at 4 sites. Of which, 4 of these subjects failed screening due to not meeting one or more inclusion/exclusion criteria.

Pre-assignment

Screening details:

A total of 4 subjects were randomized in 1:1 ratio to undergo either contrast-enhanced computed tomography (CECT) or non-enhanced computed tomography (NECT), of which 1 subject withdrew from study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Visipaque™: Contrast-Enhanced Computed Tomography (CECT)

Arm description:

Subjects received 1 intravenous injection of Visipaque™ 320 mg I/ml injection (100 mL iodixanol) and underwent computed tomography (CT) examination.

Arm type	Experimental
Investigational medicinal product name	Visipaque
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

100 mL iodixanol (Visipaque Injection 320 mg I/mL), followed by a 10 mL saline flush to ensure delivery of the full dose of Visipaque.

Arm title	Saline: Non-Enhanced Computed Tomography (NECT)

Arm description:

Subjects received 1 intravenous injection of saline placebo (matched to Visipaque™ 320 mg I/ml injection) and underwent computed tomography (CT) examination and supplemental non-contrast duplex ultrasonography imaging examination.

Arm type	Placebo
Investigational medicinal product name	Saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

100 mL saline, followed by a 10 mL saline flush.

Number of subjects in period 1	Visipaque™: Contrast-Enhanced Computed Tomography (CECT)	Saline: Non-Enhanced Computed Tomography (NECT)
Started	2	2
Completed	2	1
Not completed	0	1
Consent withdrawn by subject	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Visipaque™: Contrast-Enhanced Computed Tomography (CECT)
Reporting group description:	
Subjects received 1 intravenous injection of Visipaque™ 320 mg I/ml injection (100 mL iodixanol) and underwent computed tomography (CT) examination.	
Reporting group title	Saline: Non-Enhanced Computed Tomography (NECT)
Reporting group description:	
Subjects received 1 intravenous injection of saline placebo (matched to Visipaque™ 320 mg I/ml injection) and underwent computed tomography (CT) examination and supplemental non-contrast duplex ultrasonography imaging examination.	

Reporting group values	Visipaque™: Contrast-Enhanced Computed Tomography (CECT)	Saline: Non-Enhanced Computed Tomography (NECT)	Total
Number of subjects	2	2	4
Age categorical Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	0	0	0
>=65 years	2	2	4
Gender categorical Units: Subjects			
Female	0	0	0
Male	2	2	4
Ethnicity Units: Subjects			
Hispanic or Latino	1	0	1
Not Hispanic or Latino	1	2	3
Unknown or Not Reported	0	0	0
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	2	2	4
More than one race	0	0	0
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Visipaque™: Contrast-Enhanced Computed Tomography (CECT)

Reporting group description:

Subjects received 1 intravenous injection of Visipaque™ 320 mg I/ml injection (100 mL iodixanol) and underwent computed tomography (CT) examination.

Reporting group title	Saline: Non-Enhanced Computed Tomography (NECT)

Reporting group description:

Subjects received 1 intravenous injection of saline placebo (matched to Visipaque™ 320 mg I/ml injection) and underwent computed tomography (CT) examination and supplemental non-contrast duplex ultrasonography imaging examination.

Primary: Assessment of the Incidence of Acute Kidney Injury (AKI) Stage >=1 Per Acute Kidney Injury Network (AKIN) Serum Creatinine (SCr) Criteria

End point title	Assessment of the Incidence of Acute Kidney Injury (AKI) Stage >=1 Per Acute Kidney Injury Network (AKIN) Serum Creatinine (SCr) Criteria[1]

End point description:

AKIN Serum Creatinine Criteria for AKI- Stage 1: a SCr increase of >=0.3 mg/dL (>=26.4 µmol/L) or increase to >=150% to 200% (>=1.5- to 2.0-fold) from baseline within 48 hours. Stage 2: a SCr increase to >200% to 300% (>2.0- to 3-fold) from baseline within 48 hours. Stage 3: a SCr increase to >300% (>3.0-fold) from baseline or SCr >=4.0 mg/dL (>=354 µmol/L) with an acute increase of >=0.5 mg/dL (>=44 µmol/L) within 48 hours. The study was early terminated as limited number of subjects enrolled (N=4 randomized subjects) hence, no statistical analyses were performed, and no tables and listings were produced.

End point type	Primary

End point timeframe:

48 hours post-baseline (Follow-up 1)

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: Due to early termination of study, no statistical analyses were performed, and no tables and listings were produced.

End point values	Visipaque™: Contrast-Enhanced Computed Tomography (CECT)	Saline: Non-Enhanced Computed Tomography (NECT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: mg/dL				
number (not applicable)				

Notes:

[2] - Due to early termination of study, no tables & listings were produced to perform planned analysis.

[3] - Due to early termination of study, no tables & listings were produced to perform planned analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of the Incidence of Acute Kidney Injury (AKI) Stage >=2 Per Acute Kidney Injury Network (AKIN) Serum Creatinine (SCr) Criteria

End point title	Assessment of the Incidence of Acute Kidney Injury (AKI) Stage >=2 Per Acute Kidney Injury Network (AKIN) Serum Creatinine (SCr) Criteria

End point description:

AKIN Serum Creatinine Criteria for AKI- Stage 1: a SCr increase of >=0.3 mg/dL (>=26.4 µmol/L) or increase to >=150% to 200% (>=1.5- to 2.0-fold) from baseline within 48 hours. Stage 2: a SCr increase to >200% to 300% (>2.0- to 3-fold) from baseline within 48 hours. Stage 3: a SCr increase to >300% (>3.0-fold) from baseline or SCr >=4.0 mg/dL (>=354 µmol/L) with an acute increase of >=0.5 mg/dL (>=44 µmol/L) within 48 hours. The study was early terminated as limited number of subjects enrolled (N=4 randomized subjects) hence, no statistical analyses were performed, and no tables and listings were produced.

End point type	Secondary

End point timeframe:

48 hours post-baseline (Follow-up 1)

End point values	Visipaque™: Contrast-Enhanced Computed Tomography (CECT)	Saline: Non-Enhanced Computed Tomography (NECT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: mg/dL				
number (not applicable)				

Notes:

[4] - Due to early termination of study, no tables and listings were produced to perform planned analysis.
[5] - Due to early termination of study, no tables and listings were produced to perform planned analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of the Incidence of Acute Kidney Injury (AKI) by Contrast Induced Nephropathy (CIN)

End point title	Assessment of the Incidence of Acute Kidney Injury (AKI) by Contrast Induced Nephropathy (CIN)

End point description:

Standard definition of CIN: Increase in SCr of 0.5 mg/dL or more in the 24 to 72 hours after the CT scan. The study was early terminated as limited number of subjects enrolled (N=4 randomized subjects) hence, no statistical analyses were performed, and no tables and listings were produced.

End point type	Secondary

End point timeframe:

48 hours post-baseline (Follow-up 1)

End point values	Visipaque™: Contrast-Enhanced Computed Tomography (CECT)	Saline: Non-Enhanced Computed Tomography (NECT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: mg/dL				
number (not applicable)				

Notes:

[6] - Due to early termination of study, no tables and listings were produced to perform planned analyses.
[7] - Due to early termination of study, no tables and listings were produced to perform planned analyses.

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of the Incidence of Acute Kidney Injury (AKI) Stage >=2 By Waikar Criteria

End point title	Assessment of the Incidence of Acute Kidney Injury (AKI) Stage >=2 By Waikar Criteria

End point description:

Waikar's definitions of AKI: Stage 1: 0.3 mg/dL increase in SCr over 24 hours or a 0.5 mg/dL increase in SCr over 48 hours. Stage 2: 0.5 mg/dL increase in SCr over 24 hours or a 1.0 mg/dL increase in SCr over 48 hours. Stage 3: 1.0 mg/dL increase in SCr over 24 hours or a 1.5 mg/dL increase in SCr over 48 hours. The study was early terminated as limited number of subjects enrolled (N=4 randomized subjects) hence, no statistical analyses were performed, and no tables and listings were produced.

End point type	Secondary

End point timeframe:

48 hours post-baseline (Follow-up 1)

End point values	Visipaque™: Contrast-Enhanced Computed Tomography (CECT)	Saline: Non-Enhanced Computed Tomography (NECT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[8]	0[9]		
Units: mg/dL				
number (not applicable)				

Notes:

[8] - Due to early termination of study, no tables and listings were produced to perform planned analyses.
[9] - Due to early termination of study, no tables and listings were produced to perform planned analyses.

Statistical analyses

No statistical analyses for this end point

Secondary: All Cause Mortality and Morbidity

End point title	All Cause Mortality and Morbidity

End point description:

Mortality (all cause death) and morbidity i.e. critical events. The study was early terminated as limited number of subjects enrolled (N=4 randomized subjects) hence, no statistical analyses were performed, and no tables and listings were produced.

End point type	Secondary

End point timeframe:

From Baseline to Month 6

End point values	Visipaque™: Contrast-Enhanced Computed Tomography (CECT)	Saline: Non-Enhanced Computed Tomography (NECT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[10]	0[11]		
Units: subjects				

Notes:

[10] - Due to early termination of study, no tables and listings were produced to perform planned analyses.
[11] - Due to early termination of study, no tables and listings were produced to perform planned analyses.

Statistical analyses

No statistical analyses for this end point

Secondary: Blinded Independent Assessment of Image Quality/Diagnostic Confidence Using a 5-Point Scale

End point title	Blinded Independent Assessment of Image Quality/Diagnostic Confidence Using a 5-Point Scale

End point description:

Blinded independent assessment of image quality/diagnostic confidence using a 5-point scale. Image quality/diagnostic confidence for all imaging studies was rated on a 5-point scale from 1 (poor) to 5 (excellent).

End point type	Secondary

End point timeframe:

Month 6

End point values	Visipaque™: Contrast-Enhanced Computed Tomography (CECT)	Saline: Non-Enhanced Computed Tomography (NECT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[12]	0[13]		
Units: subjects				

Notes:

[12] - Due to early termination of study, no tables and listings were produced to perform planned analyses.

[13] - Due to early termination of study, no tables and listings were produced to perform planned analyses.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

All Adverse Events (AEs) were collected from randomization until the end of the follow-up period (Month 6) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs are study-emergent AEs that is AEs that developed/worsened during any time after randomization until end of the follow-up period (Month 6). Analysis was performed on safety population which included all participants who were randomized to receive Visipaque™ or saline placebo and had post-randomization observations.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Visipaque™: Contrast-Enhanced Computed Tomography (CECT)

Reporting group description:

Subjects received 1 intravenous injection of Visipaque™ 320 mg I/ml injection (100 mL iodixanol) and underwent CT examination.

Reporting group title	Saline: Non-Enhanced Computed Tomography (NECT)

Reporting group description:

Subjects received 1 intravenous injection of saline placebo (matched to Visipaque™ 320 mg I/ml injection) and underwent CT examination and supplemental non-contrast duplex ultrasonography imaging examination.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: There were no non- serious adverse events reported in this study.

Serious adverse events	Visipaque™: Contrast-Enhanced Computed Tomography (CECT)	Saline: Non-Enhanced Computed Tomography (NECT)	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Humerus Fracture			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (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: 5 %

Non-serious adverse events	Visipaque™: Contrast-Enhanced Computed Tomography (CECT)	Saline: Non-Enhanced Computed Tomography (NECT)	
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 April 2017	Following amendments were made: Information on the recent European Society of Cardiology (ESC) 2014 guidelines was added. •Clarification that the subset of subjects who might receive MB-102 and monitored by ORFM would be from selected sites in the USA. •Clarification on use of NSAIDs and excluded medication. •Clarification of SAE reporting, laboratory AE evaluation, and blood sampling at Follow-up 1. •Critical study events were more fully defined. •Clarification of hydration requirements and the use of intravenous (i.v.) hydration. •Clarification of procedures at screening and baseline, including timing of visits and signing of informed consent. •Definition of the per-protocol set was updated. •Minor typographical errors were corrected.
25 January 2018	•Acceptable methods of contraception were further clarified to include acceptable, but not highly effective, birth control methods in line with guidelines and informed consent. •Period of metformin discontinuation prior to the Baseline Visit was increased from 24 hours to 48 hours in line with core safety information. •Thyroid-stimulating hormone (TSH) was added to the Screening laboratory evaluation.
28 March 2018	•Potentially eligible subjects could enter this study any time during their post-Endovascular Aneurysm Repair (EVAR) follow-up, once they had passed the first imaging examination (commonly scheduled 1 month after the index EVAR), and if no complications, such as endoleaks, had been detected. Consequently, assessment for eligibility could happen years after the index EVAR, when documentation of the first imaging exam might not be available, despite subsequent follow-up examination(s) providing sufficient assurance on the stable post- EVAR status of such subjects. The changes in inclusion criteria and exclusion criterion aim to allow enrolment of otherwise eligible post-EVAR subjects in cases where documentation and evidence on the first month imaging examination were not available. The requirement for stable post-EVAR conditions (no endoleak, no clinically meaningful EVAR-related complication) was unchanged, so the characteristics of the subject population remained unchanged. •The screening period was increased from 7 days to 14 days for logistical reasons. •Recent literature reference was added. •A definition of the end of the study was added. •Clarification that randomization was in a 1:1 ratio. •Text added to clarify that the use of N-acetylcysteine was discouraged for the purpose of preventing AKI. •The period of time after which the Sponsor reserves the right to discontinue participation of a study center at which no subjects had been enrolled wasincreased from within 3 months to within 6 months of initiation. •Clarification that 'personnel who were trained in the acute management of anaphylaxis and other emergencies and who have access to appropriate clinical supplies must be immediately available for 30 minutes after dosing' was added.

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.

Study was early terminated after enrollment of 4 subjects due to very slow recruitment rates. Sample size was 4 participants instead of planned 1164 participants, hence no statistical analyses were performed, no tables and listings were produced.

Notes: