

**Clinical Study Protocol
GE-012-106**

GE Healthcare

Title: 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)

("VI-CKD Study")

REVISED TO INCORPORATE AMENDMENT A04

Sponsor

GE Healthcare Ltd. and its Affiliates (hereinafter referred to as the "Sponsor")

ClinicalTrials.gov ID: NCT03119662

EudraCT Number: 2016-001668-13

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Medical Director

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Confidentiality Statement

This protocol is provided for conducting a clinical research study. The information contained in this document is confidential and, except to the extent necessary to obtain informed consent or IEC/IRB approval, cannot be disclosed unless required by governmental regulation. Persons to whom any portion of the contents of this document is disclosed must be informed that the information is confidential and may not be further disclosed by them.

Investigator's Signature Page

I have read this protocol and all associated case report forms and agree to conduct this study in full accordance with the stipulations of the protocol described herein.

Signature

Date

Print Name

Name of Sponsor/Company: GE Healthcare Ltd. and its Affiliates	Individual Study Table Referring to Part of Dossier in Which the Individual Study or Study Table is Presented:	(For National Authority Use Only)
Name of Finished Product: Visipaque™ Injection 320 mgI/mL		
Name of Active Ingredient: Iodixanol		
Title of Study: 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)		
Protocol Number: GE-012-106		
Investigators and Study Centers: Approximately 80 sites located in the United States of America, Canada, and Europe		
Phase of Development: Phase 4		
Primary Objective:		
<ul style="list-style-type: none"> 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 patients receiving placebo and undergoing nonenhanced computed tomography (NECT) and an additional non–contrast-enhanced ultrasound imaging modality. 		
Secondary Objectives:		
<ul style="list-style-type: none"> To demonstrate the safety of i.v. iodinated iso-osmolar iodixanol (Visipaque™ Injection 320 mgI/mL) usage in CECT for CKD stage III/IV patients by evaluating the incidence of AKI stage ≥2, per AKIN SCr criteria [AKIN 2015] [Mehta et al. 2007], in patients undergoing CECT with iodixanol vs patients receiving placebo and undergoing NECT and an additional non–contrast-enhanced ultrasound imaging modality. To demonstrate the safety of i.v. iodinated iso-osmolar iodixanol (Visipaque™ Injection 320 mgI/mL) usage in CECT for CKD stage III/IV patients by evaluating the incidence of AKI by other definitions (standard definition of contrast induced nephropathy (CIN) [Mehran and Nikolsky 2006], and AKI stages ≥2 by Waikar criteria [Waikar and Bonventre 2009]) in patients undergoing CECT with iodixanol vs patients receiving placebo and undergoing NECT and an additional non–contrast-enhanced ultrasound imaging modality. To demonstrate the safety of i.v. iodinated iso-osmolar iodixanol (Visipaque™ Injection 320 mgI/mL) usage in CECT for CKD stage III/IV patients by evaluating mortality and morbidity within 6 months of intervention in patients undergoing CECT with iodixanol vs. patients receiving placebo and undergoing NECT and an additional non–contrast-enhanced ultrasound imaging modality. To assess image quality/diagnostic confidence of CECT and NECT plus Ultrasound. 		
Exploratory Objectives:		
<ul style="list-style-type: none"> [REDACTED] 		

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Study Design:

This parallel-group, randomized, placebo-controlled study will examine the incidence and severity of AKI in patients with CKD stage III/IV following an i.v. injection of iso-osmolar iodinated contrast material iodixanol (Visipaque™ Injection 320 mgI/mL), as compared with patients who did not receive contrast medium during their scheduled post-EVAR surveillance imaging.

The patient population under investigation in this study is defined as outpatients who have undergone a successful EVAR procedure, are now due a routine post-procedural imaging surveillance assessment, and have already completed their first-month post procedural surveillance exam and no endoleak has been detected.

The patients will be randomly assigned in a 1:1 ratio to undergo either CECT or NECT for this routine surveillance CT examination. This randomization of EVAR patients is justified by the clinical equipoise between surveillance protocols that are routinely used in the follow-up of this patient population.

Patients randomized to the CECT arm will receive 100 mL iodixanol (Visipaque™ Injection 320 mgI/mL) prior to the scheduled CT examination.

Patients randomized to the NECT arm will receive 100 mL saline placebo intravenously prior to a scheduled CT examination and supplemental non-contrast duplex ultrasonography imaging examination. The duplex ultrasound imaging procedure will follow NECT scanning, ideally on the same day as the NECT imaging and within 2 days of performing the NECT.

All patients (CECT and NECT arms) will receive oral hydration of 500 mL of fluids following collection of blood samples for central analysis of SCr and prior to scanning. All patients (CECT and NECT arms) will need to drink at least 2500 mL fluids in the 24 hours immediately following CT scanning. In case of concern about the patient's compliance and/or capability to follow the oral hydration instructions, i.v. administration of isotonic crystalloid solution (saline or bicarbonate) may be considered. Decision on use of i.v. hydration will be made and documented before randomization and implemented regardless of whether the subject is randomized to the NECT or CECT arm. The use of *N*-acetylcysteine (NAC) is discouraged for the purpose of preventing AKI.

Follow-ups will take place at 48 hours, 7 days, and 6 months post-baseline. At Follow-up 1 (48 hours ±6 hours), blood samples will be collected either at the patient's home (if this service is available locally) or at the study center and concomitant medications, adverse events (AEs), serious adverse events (SAEs) and critical events recorded either by telephone (for patients receiving a home visit) or at the study center. If NephroCheck® biomarker analysis will be performed, urine samples will be collected. Follow-up 2 (7 days ±2 days) will be a clinic visit for those patients who meet primary criteria (AKI stage ≥1, per AKIN) at Follow-up 1 and a telephone follow-up for all other patients. At Follow-up 3 (6 months ±2 weeks), a blood sample for SCr will be collected either at the patient's home (if this service is available locally) or at the study center and concomitant medications, SAEs, AEs and critical events will be recorded either by telephone (for patients receiving a home visit) or at the study center.

Local laboratories will be used for determination of eligibility for the trial and for stratification during randomization. A central laboratory will be utilized for analysis of SCr, cystatin C, and N-GAL collected at the Baseline Visit, Follow-Up 1, Follow-Up 2 (for patients meeting primary AKIN criteria at Follow-Up 1), and Follow-Up 3 (SCr only). For patients where local NephroCheck® testing is available a urine sample will be collected for analysis of NephroCheck® biomarkers (TIMP-2 and IGFBP-7) at the Baseline Visit, 4 hours post scan and Follow-Up 1.

The addition of supplemental duplex ultrasound for the NECT arm has been selected to ensure that possible vascular complications, such as endoleaks, are not missed due to imaging without contrast, with the objective of affirming the diagnostic confidence of the post-surveillance protocol.

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CT and ultrasound images will be read at the site according to usual clinical practice to facilitate patient management decisions. The images will also be read by independent blinded readers appropriately qualified in abdominal imaging to assess image quality/diagnostic confidence. Each CECT image or NECT image plus duplex ultrasonography image will be read by 3 independent readers randomly selected from a panel of readers. Image quality/diagnostic confidence for all imaging studies will be rated on a 5-point scale from 1 (poor) to 5 (excellent).

This visual assessment is being conducted to ensure trust in the delineation of any pathologic findings to support the clinical care pathway in post EVAR surveillance.

The primary outcome measure in this study will be the incidence of AKI stage ≥ 1 (in accordance with AKIN SCr criteria [[AKIN 2015](#)] [[Mehta et al. 2007](#)])

Secondary outcome measures will include:

- Assessing the incidence of AKI stage ≥ 2 (in accordance with AKIN SCr criteria).
- Assessing the incidence of AKI by other definitions (standard definition of CIN [[Mehran and Nikolsky 2006](#)] and AKI stages ≥ 2 by Waikar criteria [[Waikar and Bonventre 2009](#)]).
- Assessing the incidence of AKI related morbidity and mortality at 6 months (Follow-Up 3). This will be assessed by an independent Critical Events Adjudication Committee (CEAC). The independent CEAC will be appointed at the commencement of the study before any patients are enrolled.
- Assessment of image quality/diagnostic confidence.

Exploratory outcome measures will include:

- Changes in SCr, cystatin C, N-GAL, and NephroCheck® biomarkers from baseline up to 48 hours post contrast/saline infusion.
- Determination of GFR as measured by an ORFM in a subset of patients.

A Steering Committee will oversee the study conduct. In addition to the Steering Committee, a Critical Event Adjudication Committee (CEAC) will be established to review all morbidity and mortality events (i.e. critical events, including EVAR-related post-baseline events). A Data Safety Monitoring Board (DSMB) will be established to periodically review AKI rates and make recommendations on the continuation of the study or potential requirement to amend the protocol. The Steering Committee and CEAC will not be provided access to any unblinded data during the conduct of the study.

Selection of Patients:
Inclusion Criteria:
 Patients may be included in the study if they meet all of the following criteria.

- (1) Is ≥ 18 years of age at the time that written informed consent is obtained.
- (2) Is male or is a nonpregnant, nonlactating female who is either surgically sterile (has a documented bilateral tubal ligation or oophorectomy and/or documented hysterectomy) or is postmenopausal (cessation of menses for more than 1 year). Women of childbearing potential must use adequate contraception* from Screening until 30 days after the Baseline Visit and must have a negative result for a urine human chorionic gonadotropin pregnancy test at the Baseline Visit.
- (3) Is an outpatient who has undergone successful EVAR and is scheduled for his/her next post-procedural imaging follow-up examination.
- (4) Has previously completed one or more of his or her post-EVAR surveillance imaging examination(s) that provided evidence on stable post-EVAR status.
- (5) Has a documented diagnosis of stage III or IV (defined as $30 \leq$ estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² and $15 \leq$ eGFR < 30 mL/min/1.73 m², respectively, according to the Modification of Diet in Renal Disease [MDRD] equation) CKD and stable renal function (last 2 SCr

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values within ± 0.5 mg/dL of each other, with the most recent value within 14 days prior to the scheduled CT examination and the preceding value within 1 to 12 months before that).

(6) Is able to provide written informed consent.

(7) Is able and willing to comply with all study procedures as described in the protocol.

* Adequate contraception is based on those methods identified in the Clinical Trial Facilitation Group document [\[CTFG Guidance 2014\]](#) for clarification of effective contraception. Such methods include: combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal); progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable); intrauterine device; intrauterine hormone-releasing system; bilateral tubal occlusion; vasectomized partner; sexual abstinence, progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, male or female condom with or without spermicide cap, diaphragm or sponge with spermicide (refer to Section 8.6).

Exclusion Criteria:

Patients must be excluded from participating in this study if they meet any of the following criteria

- (1) Is pregnant, lactating, is possibly pregnant, or is actively trying to conceive during the study period.
- (2) Is a patient for whom an endoleak or other clinically meaningful EVAR-related complication (as judged by the investigator) has already been discovered.
- (3) Is a patient who is undergoing surveillance following a Thoracic Endovascular Repair (TEVAR)
- (4) Has a known or suspected history of immediate or delayed hypersensitivity (including but not limited to hives, anaphylactoid or cardiovascular reactions, laryngeal edema, and bronchospasm) to iodine or any iodinated contrast medium.
- (5) Is using metformin (e.g., Glucophage®) that cannot be discontinued for the period of 48 hours prior to the Baseline Visit and for at least 48 hours after the imaging procedure (renal function must be evaluated before metformin is resumed).
- (6) Has been exposed to any intravascular iodinated contrast medium in the 14 days prior to the Baseline Visit.
- (7) Has congestive heart failure (New York Heart Association [NYHA] Class IV) or hepatic failure/liver cirrhosis according to the investigator's judgement.
- (8) Has stage V CKD, defined as eGFR < 15 mL/min/1.73 m² according to the MDRD equation.
- (9) Has a pre-existing requirement for renal dialysis.
- (10) Has undergone percutaneous transluminal renal angioplasty (PTRA) within 12 months before the index EVAR procedure or is scheduled to undergo PTRA during the study period.
- (11) Has any clinically active, serious, life-threatening disease, medical, or significant psychiatric condition; has a life expectancy of less than 6 months; or is, in the Investigator's opinion, unsuitable for participation in the study for any reason.
- (12) Has been enrolled in another clinical study within the 30 days prior to the Screening Visit or is planned to enroll in another clinical study within the duration of this study.
- (13) Has been previously enrolled in this study.
- (14) Is using i.v. vasopressor or inotropic medications.
- (15) Has used nonsteroidal anti-inflammatory drugs (NSAIDs) or any nephrotoxic medication within 48 hours of the Baseline Visit or will do so within 72 hours after the CT procedure (renal function must be evaluated before any nephrotoxic medication is resumed) – with the exception of acetylsalicylic acid (Aspirin) at a dose of ≤ 100 mg daily (QD).
- (16) Has been hospitalized within 30 days prior to Screening Visit for any reason other than practical purposes for management of tests or diagnostic assessments.

Number of Patients/Centers Planned: 1164 patients randomized at approximately 80 centers.

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Treatment of Patients:

Investigational Medicinal Product: 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.

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

Duration of the Study: Approximately 6 months in total for each subject, comprising a Screening Visit, Baseline Visit (Clinic Visit), Follow-Up 1 (48 hours post-baseline), Follow-Up 2 (7 days post-baseline), plus a Follow-Up 3 at 6 months post-Baseline Visit.

Efficacy and Safety Variables

Primary Endpoint:

- Incidence of AKI stage ≥ 1 (AKIN SCr criteria) following an i.v. injection of iodinated iso-osmolar contrast material iodixanol (Visipaque™ Injection 320 mgI/mL) or saline in patients with CKD stage III/IV assessed at 48 hours post-baseline (Follow-up 1).

Secondary Endpoints:

AKI Secondary Endpoints

- Incidence of AKI stage ≥ 2 (by AKIN SCr criteria) following an i.v. injection of iodinated iso-osmolar contrast material iodixanol (Visipaque™ Injection 320 mgI/mL) or saline in patients with CKD stage III/IV assessed at 48 hours post-baseline (Follow-up 1).
- Incidence of AKI (by standard definition of CIN [Mehran and Nikolsky 2006]) following an i.v. injection of iodinated iso-osmolar contrast material iodixanol (Visipaque™ Injection 320 mgI/mL) or saline in patients with CKD stage III/IV assessed at 48 hours post-baseline (Follow-up 1).
- Incidence of AKI stage ≥ 2 (by Waikar criteria [Waikar and Bonventre 2009]) following i.v. administration of iodinated iso-osmolar contrast material iodixanol (Visipaque™ Injection 320 mgI/mL) or saline in patients with CKD stage III/IV assessed at 48 hours post-baseline (Follow-up 1).

Other Secondary Endpoints

- Mortality and morbidity (i.e. critical events, including EVAR-related post-baseline events, as adjudicated by the CEAC) assessed at 6 months (Follow-up 3) in patients with CKD stage III/IV.
- Blinded independent assessment of image quality/diagnostic confidence using a 5-point scale.

All primary and secondary endpoints will be analyzed by CKD stage III and stage IV independently in addition to the collective stage III/IV group analyses.

Exploratory Endpoints:

- [REDACTED]
- [REDACTED]
- [REDACTED]

Other Safety Evaluations:

The following safety variables will be monitored:

- Occurrence of AEs and SAEs up to 6 months.
- Vital signs (sitting): blood pressure, heart rate, respiratory rate.
- Physical examination findings.

Definitions:

CKD staging [National Kidney Foundation 2002] [Kirsztajn 2009]:

Stage I: kidney damage with normal or high GFR (≥ 90 mL/min/1.73 m²).

Stage II: kidney damage with mildly decreased GFR (60-89 mL/min/1.73 m²).

Stage IIIA: moderately reduced kidney function (GFR 45-59 mL/min/1.73 m²).

Stage IIIB: moderately reduced kidney function (GFR 30-44 mL/min/1.73 m²).

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<p>Stage IV: severely reduced kidney function (GFR 15-29 mL/min/1.73 m²).</p> <p>Stage V: very severe or end-stage kidney failure (GFR <15 mL/min/1.73 m²) or on dialysis.</p> <p>AKIN Serum Creatinine Criteria for AKI [AKIN 2015]:</p> <p>Stage 1: a SCr increase of ≥ 0.3 mg/dL (≥ 26.4 μmol/L) or increase to $\geq 150\%$ to 200% (≥ 1.5- to 2.0-fold) from baseline within 48 hours.</p> <p>Stage 2: a SCr increase to $>200\%$ to 300% (>2.0- to 3-fold) from baseline within 48 hours.</p> <p>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.</p> <p>Standard definition of CIN [Mehran and Nikolsky 2006]:</p> <p>Increase in SCr of 0.5 mg/dL or more in the 24 to 72 hours after the CT scan.</p> <p>Waikar's definitions of AKI [Waikar and Bonventre 2009]:</p> <p>Stage 1: 0.3 mg/dL increase in SCr over 24 hours or a 0.5 mg/dL increase in SCr over 48 hours.</p> <p>Stage 2: 0.5 mg/dL increase in SCr over 24 hours or a 1.0 mg/dL increase in SCr over 48 hours.</p> <p>Stage 3: 1.0 mg/dL increase in SCr over 24 hours or a 1.5 mg/dL increase in SCr over 48 hours.</p> <p>Full Analysis Set (FAS): All patients who receive Visipaque™ or saline placebo and have both baseline and post-scan SCr measurements.</p> <p>Safety population: All patients who are randomized to receive Visipaque™ or saline placebo and have post-randomization observations.</p> <p>Statistical Methods and Planned Analysis:</p> <p>The primary, secondary and exploratory analyses will be performed using the FAS population. Mortality and morbidity (i.e. critical events, including EVAR-related post-baseline events, as adjudicated by the CEAC), image quality, and other safety outcome measures will be evaluated in the safety population.</p> <p>Primary Analysis:</p> <p>With P1 defined as the incidence of AKI stage ≥ 1 48 hours after i.v. administration of the iodinated iso-osmolar contrast material iodixanol (Visipaque™ Injection 320 mg-I/mL) and P2 defined as the incidence rate of AKI stage ≥ 1 48 hours after administration of saline placebo, the primary hypothesis to be tested for the primary analysis in the FAS is:</p> <p>H_0: $P1 - P2 \geq 0.05$</p> <p>H_1: $P1 - P2 < 0.05$</p> <p>A 2-sided 95% CI for noninferiority testing will be computed for the difference in sample incidence rates for the 2 treatment groups (CECT vs NECT, for the stage III and IV CKD patients combined) by using the Miettinen and Nurminen method. If the upper bound of the 95% confidence interval (CI) is less than 5%, then the noninferiority of Visipaque™ to the control (saline) will be concluded. In addition, the incidence rates and associated 95% CIs for the 2 treatment groups stratified by CKD stage will be reported.</p> <p>Secondary Analyses:</p> <p>The secondary hypothesis to be tested for the secondary endpoints that are proportions is the following:</p> <p>H_0: $P1 - P2 \geq 0.05$</p> <p>H_1: $P1 - P2 < 0.05$</p> <p>The secondary hypotheses will be tested in patients in the FAS with CKD stage III and IV combined. The incidences for the 2 treatment groups (CECT vs NECT) will be compared by using the same statistical method as for the primary analysis.</p> <p>AKI Secondary Endpoint Analyses:</p> <p>The secondary endpoints of the study are:</p>		

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- Incidence of AKI stage ≥ 2 (by AKIN SCr criteria [AKIN 2015] [Mehta et al. 2007]) following an i.v. injection of iodinated iso-osmolar contrast material iodixanol (Visipaque™ Injection 320 mg I/mL) or saline in patients with CKD stage III or IV. This analysis will be performed for the FAS assessed at 48 hours post-baseline (Follow-up 1).
- Incidence of AKI (by standard definition of CIN [Mehran and Nikolsky 2006]) following an i.v. injection of iodinated iso-osmolar contrast material iodixanol (Visipaque™ Injection 320 mg I/mL) or saline in patients with CKD stage III or IV. This analysis will be performed for the FAS assessed at 48 hours post-baseline (Follow-up 1).
- Incidence of AKI stage ≥ 2 (by Waikar criteria [Waikar and Bonventre 2009]) following i.v. administration of iodinated iso-osmolar contrast material iodixanol (Visipaque™ Injection 320 mg I/mL) or saline in patients with CKD stage III or IV. This analysis will be performed for the FAS assessed at 48 hours post-baseline (Follow-up 1).

In order to control the false positive rate at a one-sided 0.025 level across the testing of the secondary endpoints, the above endpoints will be tested hierarchically in the order given above. Each endpoint will be tested at a one-sided 0.025 level of significance; when a statistical test for a given endpoint fails to reach statistical significance in the appropriate direction, testing on all remaining secondary endpoints in the hierarchy will cease and the study will be considered successful on all secondary endpoints up to that point.

Other Secondary Endpoint Analyses:

Mortality and morbidity:

- All-cause death assessed at 6 months (Follow-up 3).
- Critical events (including EVAR-related post-baseline events) assessed at 6 months (Follow-up 3).
- Incidence rate of hospitalization due to renal failure assessed at 6 months (Follow-up 3).
- Incidence of requirement for renal replacement therapy (i.e., renal transplant, dialysis, or hemofiltration/ultrafiltration) assessed at 6 months (Follow-up 3).
- Incidence of the composite of death and hospitalization events due to renal failure assessed at 6 months (Follow-up 3).
- Hospital length of stay (LOS) in days assessed at 6 months (Follow-up 3).
- Incidence rate of patients with $\geq 30\%$ reduction in eGFR at 48 hours compared to baseline.
- Other criteria defined by the CEAC.

Among the mortality and morbidity events, binary variables will be analyzed using the noninferiority test for proportions described above. Hospital LOS will be summarized descriptively by arm.

Image quality/diagnostic confidence will be rated on a scale of 1 to 5. The frequency distribution of image-quality/diagnostic confidence ratings will be summarized for each type of imaging procedure in each treatment arm. Thus, there will be 2 separate summaries of image quality/diagnostic confidence ratings, CECT and NECT plus non-contrast duplex ultrasonography images. Both by-reader and majority-read analyses will be performed for each summarization.

The image-quality/diagnostic confidence ratings will be analyzed based on individual scores and will also be dichotomized as evaluable (rating of 3 to 5) or nonevaluable (rating of 1 or 2). The frequency distribution of evaluable vs. nonevaluable image quality/diagnostic confidence ratings will be summarized for each treatment group. Thus, there will be 2 separate summaries of image quality/diagnostic confidence ratings: CECT and NECT plus non-contrast duplex ultrasonography. Both by-reader and majority-read analyses will be performed for each summarization.

In addition, the above analyses will be repeated for the stage III CKD subgroup and the stage IV CKD subgroup separately.

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For a randomly selected subset of 5% of the patients (N=29 in each arm), the images will undergo a second blinded visual assessment by the same reader. Intra-reader (within-reader) agreement for these blinded visual image assessments will be measured by percentage agreement. A percentage agreement with an exact 95% CI will be determined for each reader comparison and all readers for subjects with re-reads of images. In cases where images are re-read, it is the result of the first read that is to be included in the image quality/diagnostic confidence summaries.

Exploratory Analyses:

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Safety Analyses:

Incidence rate of adverse clinical events assessed at 6 months, the mean change from baseline to post-baseline vital signs, and the physical examinations will be summarized for the 2 treatment groups.

Sample Size Estimation:

The primary endpoint is the incidence rate (proportion) of AKI stage ≥ 1 (by AKIN SCr criteria) at 48 hours after intervention in patients with stage III or stage IV CKD. With P1 defined as the incidence rate of AKI stage ≥ 1 following i.v. administration of Visipaque™ and P2 defined as the incidence rate of AKI stage ≥ 1 following administration of placebo, the sample size estimate is based on the following assumptions and statistical method:

- Both P1 and P2 are 10%
- A noninferiority margin of 5%
- Power of 80% using the 95% CI of P1 – P2
- The score test [\[Miettinen and Nurminen 1985\]](#) with a 1-sided 0.025 significance level is employed

A sample size of 1164 randomized patients (582 per treatment group) in the FAS will provide 80% power to demonstrate noninferiority of the proportion of AKI stage ≥ 1 (by AKIN criteria) in patients receiving Visipaque™ Injection 320 mgI/mL as compared with patients receiving the saline placebo.

To compensate for a screen failure rate of approximately 15%, approximately 1370 patients will be screened. A blinded sample size re-estimation will be performed after 50% of patients are enrolled and adjudicated by the CEAC. The calculation will be conducted by an independent statistician and will be based on the blinded, overall rate of AKI as determined by the CEAC. The purpose of this re-evaluation is to confirm assumptions made about the rate of AKI in the planned sample size calculation.

2 TABLE OF CONTENTS

2.1 Overall Table of Contents

	Page Number
1 SYNOPSIS	3
2 TABLE OF CONTENTS	11
2.1 Overall Table of Contents	11
2.2 List of Tables	14
2.3 List of Figures.....	14
3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS	15
4 BACKGROUND INFORMATION AND STUDY RATIONALE	17
5 STUDY OBJECTIVES AND PURPOSE	20
6 STUDY DESIGN	22
6.1 Overall Study Design and Plan.....	22
6.2 Study Timeframe	25
6.3 Risks and Benefits to Patients	25
7 SELECTION AND WITHDRAWAL OF PATIENTS.....	27
7.1 Patient Selection	27
7.2 Inclusion Criteria	27
7.3 Exclusion Criteria.....	28
7.4 Withdrawal and Termination Criteria.....	29
7.4.1 Patient Withdrawal	29
7.4.2 Study or Site Termination	29
8 TREATMENT OF PATIENTS	30
8.1 Investigational Medicinal Product (IMP)	30
8.1.1 Visipaque™ Injection.....	30
8.1.2 Comparator (Placebo).....	30
8.1.3 Optical Renal Function Monitoring.....	30
8.1.4 IMP Accountability	31
8.1.5 Registration of Investigational Medicinal Product(s) Complaints ..	31
8.2 Method of Numbering Patients and Assigning Patients to Treatment Groups	31
8.3 Selection of Doses and Timing.....	32
8.4 Blinding	32
8.5 Prior and Concurrent Medications or Procedures	32
8.6 Contraception and Pregnancy Avoidance Procedure	33
8.7 Treatment Compliance	34

9	STUDY PROCEDURES	35
9.1	Screening Visit	38
9.2	Baseline Visit.....	39
9.2.1	Image Acquisition	41
9.2.2	Duplex Ultrasonography Imaging	41
9.2.3	Optical Renal Function Monitoring.....	41
9.3	Follow-Up 1.....	41
9.4	Follow-up 2	42
9.5	Follow-up 3	42
9.6	Steering Committee	43
9.7	Critical Events Adjudication Committee.....	43
9.8	Data Safety Monitoring Board	44
9.9	Image Interpretation	44
10	EFFICACY, SAFETY, AND OTHER VARIABLES	46
10.1	Endpoints.....	46
10.1.1	Primary Endpoint.....	46
10.1.2	Secondary Endpoints	46
10.1.3	Exploratory Endpoints.....	46
10.2	Safety Assessments	47
10.2.1	Clinical Laboratory Evaluation	47
10.2.2	Vital Signs	49
10.2.3	ECG	49
10.2.4	Physical Examination	50
10.2.5	Critical Study Events	50
10.2.6	Adverse Events	50
10.2.7	Serious Adverse Events	52
10.2.8	Other Significant Adverse Events	52
10.2.9	Adverse Event and Serious Adverse Event Reporting	52
10.2.10	Urgent Safety Measures.....	54
10.2.11	Pregnancy Reporting	54
10.3	Other Variables.....	55
10.3.1	Demographic Data.....	55
10.3.2	Medical and Surgical History	55
10.3.3	Prior and Concomitant Medication and Procedures	55
10.4	Appropriateness of Measurements	55
11	DATA HANDLING AND QUALITY ASSURANCE.....	56
11.1	Completing and Signing Case Report Forms	56
11.2	Clinical Data Management	56
11.3	Archiving	56
12	STATISTICAL METHODS AND PLANNED ANALYSIS	57
12.1	General Statistical Considerations.....	57
12.2	Definitions	57
12.3	Populations for Analysis.....	58
12.3.1	Determination of Safety Population	58

12.3.2	Determination of Full Analysis Set	58
12.3.3	Determination of Per-Protocol Set	58
12.4	Patient Demographics/Other Baseline Characteristics	59
12.5	Study Treatments	59
12.6	Primary Analysis	59
12.6.1	Variable	59
12.6.2	Statistical Hypothesis, Model, and Method of Analysis	59
12.6.3	Handling of Missing Values/Censoring/Discontinuations	60
12.6.4	Supportive Analyses	60
12.7	Secondary Analyses	60
12.7.1	Secondary Variables and Analyses	60
12.7.2	Exploratory Analyses	62
12.7.3	Other Safety Variables and Analyses	63
12.8	Sample Size Calculation	64
12.9	Procedures for Missing, Unused, and Spurious Data	65
12.10	Rules for Excluding Patients from Analysis	65
12.11	Procedures for Reporting Deviations from Original Statistical Plan	65
13	SPECIAL REQUIREMENTS AND PROCEDURES	66
13.1	Regulatory, Institutional and Ethical Review	66
13.2	Investigator's Responsibilities	66
13.2.1	Overall Responsibilities	66
13.2.2	Patient Informed Consent	66
13.2.3	Direct Access to Source Data/Documents	67
13.2.4	Confidentiality Regarding Study Patients	67
13.3	Protocol Deviations	67
13.4	Study Monitoring	67
13.5	Audit and Inspection	68
13.6	Insurance	68
13.7	Publication Policy	68
14	REFERENCES	69
15	APPENDICES	72
15.1	Information on Investigational and Registered Products	72
15.2	Equipment Parameters	72
15.3	Normal Limits for Vital Signs	72
16	CLINICAL PROTOCOL AMENDMENT SUMMARIES	73
16.1	Amendment A01	73
16.1.1	Reasons for Amendment	73
16.1.2	Description of Changes	73
16.2	Amendment A02	93
16.2.1	Reasons for Amendment	93
16.2.2	Description of Changes	93
16.3	Amendment A03	97
16.3.1	Reasons for Amendment	97

	16.3.2	Description of Changes	97
16.4		Amendment A04	107
	16.4.1	Reasons for Amendment	107
	16.4.2	Description of Changes	108

2.2 List of Tables

Table 1	Study Schedule of Events	36
Table 2	Clinical Laboratory Parameters	48
Table 3	Criteria for Normal Limits for Vital Signs	72

2.3 List of Figures

Figure 1	Study Diagram	24
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3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
AKI	Acute kidney injury
AKIN	Acute kidney injury network
ANOVA	Analysis of variance
CEAC	Critical Events Adjudication Committee
CECT	Contrast-enhanced computed tomography
CI	Confidence interval
CIN	Contrast-induced nephropathy
CKD	Chronic kidney disease
eCRF	Electronic Case report form
CRO	Contract research organization
CT	Computed tomography
CTA	Computed tomography angiography
CTFG	Clinical Trial Facilitation Group
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EVAR	Endovascular aneurysm repair
FAS	Full analysis set
GFR	Glomerular filtration rate
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IGFBP-7	Insulin-Like Growth Factor Binding Protein 7
IMP	Investigational medicinal product
IRB	Institutional/Independent Review Board
i.v.	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system
LOS	Length of stay
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
NECT	Nonenhanced computed tomography
N-GAL	Neutrophil gelatinase-associated lipocalin
NSAID	Nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
ORFM	Optical renal function monitor
PP	Per-protocol
QD	Daily
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCr	Serum creatinine
SD	Standard deviation

SOPs	Standard operating procedures
sTSH	Supersensitive thyroid-stimulating hormone
TIMP-2	Tissue inhibitor of metalloproteinases-2
TSH	Thyroid-stimulating hormone
US	Ultrasound
WBC	White blood cell

4 BACKGROUND INFORMATION AND STUDY RATIONALE

Chronic kidney disease (CKD) is the slow loss of kidney function over time. CKD can result from many different causes, including genetic disorders (polycystic kidney disease), autoimmune disorders (e.g., systemic lupus erythematosus and scleroderma), circulatory problems, injury or infection, and the toxic effects of many drugs and other chemicals. CKD is a substantial public health concern in the United States because 1 in 10 American adults, more than 20 million people, have some level of CKD [NIDDKD 2016]. As the glomerular filtration rate (GFR) declines, the kidneys become more sensitive to the potentially nephrotoxic effects of various drugs or other products.

For decades, patients with significant CKD have been considered to be at high risk for contrast-induced nephropathy (CIN), which is defined as acute kidney injury (AKI) after exposure to intravascular iodinated contrast media [Valette et al 2012]. Thus, the use of iodinated contrast media in such patients has been severely limited, even though iodinated contrast media are important diagnostic agents that can improve diagnostic accuracy and ultimately improve patient care.

A causal relationship between iodinated contrast medium exposure and AKI has been presumed based on early studies in patients undergoing excretory urography using high-osmolar contrast media and from studies in patients who have undergone cardiac catheterizations examinations (intra-arterial route) that expose the kidneys to atheroemboli from aortic plaques and a peak concentration of iodinated contrast in renal arterial blood [Ahmed and Newhouse 2013]. However, the conclusions of such studies may not be generalizable to contrast-enhanced computed tomography (CECT) examinations, which involve the intravenous (i.v.) administration of low-osmolar or iso-osmolar contrast media. Also, many studies of post-contrast renal dysfunction focused on hospitalized patients, who are likely to have other risk factors for nephrotoxicity. A retrospective study of the electronic medical records of patients hospitalized at an academic medical center showed that the incidence of increased serum creatinine (SCr) in patients who did not receive iodinated contrast material was similar to the incidences found in studies of CIN [Newhouse et al 2008]. In the absence of an appropriate control group, SCr increases could have been incorrectly ascribed to the iodinated contrast medium.

Only a few, nonrandomized studies of CIN have included a control group. In those studies, the rate of AKI tended to be paradoxically higher in the control group, probably because the clinicians had avoided administering i.v. iodinated contrast medium to patients who were considered to be at increased risk for AKI because of other risk factors for nephrotoxicity or because the patients had recently had an acute change in renal function [McDonald et al 2013a].

Most of the subjects in most of the controlled studies of CIN have normal or only mildly impaired renal function (stage I or II CKD); these patients may not be at particularly high risk of CIN, and SCr may be a particularly insensitive marker of acute renal impairment in patients with a large functional reserve. Because of the historic reluctance to administer iodinated contrast medium to patients at high risk of kidney injury, patients who may be at the highest

risk of kidney injury are rarely included in studies of the incidence of CIN or may be included only in the control group that did not receive contrast medium [Davenport et al 2014].

The study of CIN is further confounded by the numerous definitions of CIN [Davenport et al 2014]. Absolute (e.g., 0.3 or 0.5 mg/dL) and percentage (e.g., 25%, 50%, or 100%) increases in SCr values have been used, in isolation or in combination. As a result, the reported incidence of CIN has ranged widely, depending on the degree of baseline renal impairment, the use of a control group, and the chosen definition of CIN.

Four large retrospective studies in which subjects were matched or stratified by propensity score have recently been published. Two studies by Davenport et al [Davenport et al 2013a] [Davenport et al 2013b] found i.v. low-osmolar and iso-osmolar contrast medium to be an independent risk factor for nephrotoxicity in patients with severe chronic renal impairment (the risk of nephrotoxicity increased progressively as renal function declined). The other 2 studies by McDonald et al [McDonald et al 2013b] [McDonald et al 2015] concluded that i.v. low-osmolar or iso-osmolar contrast medium may not be the causative agent in diminished renal function after contrast medium i.v. administration. More specifically, among patients at the highest perceived risk of post contrast AKI (throughout the entire spectrum of CKD, including stages III-V), i.v. administration of iodixanol for CECT was not an independent risk factor for AKI, dialysis, or mortality [McDonald et al. 2017].

There is a need for prospective, randomized trials including a control group (i.e., subjects not receiving iodinated contrast medium) to assess more reliably the influence of low-osmolar or iso-osmolar contrast medium on AKI incidence in patients with chronic renal impairment [Davenport et al 2014]. No randomized trials have been performed thus far due to difficulty in performing them and possible ethical concerns. Patients undergoing post-endovascular aneurysm repair (EVAR) surveillance would be an appropriate population in which to perform a study because approximately 30% of them have renal impairment and because there is no universally accepted imaging protocol involving CECT for their surveillance.

There is a need to explore the renal safety of the i.v. administration of the iso-osmolar contrast medium iodixanol (Visipaque™ Injection 320 mg I/ml) in patients with chronic renal impairment. Many clinicians have been avoiding the use of iodinated contrast material for patients with kidney disease because of the presumption that these agents pose a risk of nephrotoxicity in patients with compromised renal function. This abundant, but also controversial, literature has led to the avoidance of using i.v. iodinated contrast media in patients with stages III and IV CKD because of the continued fear of inducing CIN. Even when rigorous hydration protocols and concomitant pre-medication are used in an attempt to prevent CIN [Briguori and Marenzi 2006] [Mueller 2006], many physicians still deny patients access to contrast media and consequently fail to generate critical and highly valuable diagnostic information. In addition, the safety of i.v. use of iodinated contrast media for CECT in patients with stage III or IV CKD has not been addressed in randomized controlled trials, and the existing controlled studies have been marred by the lack of randomization. As a result, it is unclear whether the risk of nephrotoxicity from the contrast medium outweighs the benefits of the information that would be obtained from the CECT. In this clinical trial, which will be a randomized placebo-controlled noninferiority study, GE Healthcare will assess renal safety of the i.v. administration of iso-osmolar iodixanol (Visipaque™ Injection 320 mg I/ml)

in patients who have stage III or IV CKD and are undergoing radiologic surveillance after an EVAR procedure. The randomization of patients to receive either CECT or an examination that does not involve contrast medium (nonenhanced computed tomography [NECT] plus non-contrast duplex ultrasonography) is justifiable because the relative value of the two approaches for post-EVAR surveillance cannot yet be made on the basis of the available evidence.

There is no universally accepted imaging protocol for post-EVAR surveillance (e.g., for detection of endoleaks, detection of mechanical changes in the stent-graft, and evidence of expansion or shrinkage of the residual sac). The American College of Radiology notes that computed tomography angiography (CTA) is considered the gold standard for the diagnosis of endoleaks [ACR 2012]. In 2010, the Society of Interventional Radiology published clinical practice guidelines for EVAR [Walker et al 2010]. These guidelines, which were endorsed by the Cardiovascular and Interventional Radiological Society of Europe and the Canadian Interventional Radiology Association, indicated that even though CTA is the most commonly used examination for post-EVAR surveillance, unenhanced CT, magnetic resonance angiography, ultrasonography, and even simple radiography, remain commonly used and appropriate. The recent ESC 2014 Guideline on the diagnosis and treatment of aortic diseases is also largely in line with guidelines published earlier in terms of imaging follow-up recommendations, and the use of color-Doppler ultrasound (US) can be considered as an alternative in case neither endoleak nor abdominal aortic aneurysm sac enlargement was documented during the first year after EVAR [ESC Guidelines 2014]. In practice, vascular surgeons do not always follow these guidelines; and if the results of the first post-EVAR CTA are negative, unenhanced CT or US exams are often ordered instead of CTA for continued surveillance. Thus, after the first post-EVAR examination, there is clinical equipoise between imaging methods that do and do not require administration of contrast medium. As a result, it is ethically acceptable to use randomization to assign some patients to receive contrast medium and some patients to be evaluated without the use of contrast medium.

The present study is a randomized, placebo-controlled noninferiority trial of the renal safety of iodixanol (Visipaque™ Injection 320 mg I/ml), which is an iso-osmolar iodinated contrast material, in patients who have CKD stage III or IV and are undergoing radiologic surveillance after an EVAR procedure. SCr and other biomarkers of renal function will be assessed before and within 2 days after i.v. administration of iodixanol or saline placebo; morbidity and mortality will be assessed at 6 months.

5 STUDY OBJECTIVES AND PURPOSE

The primary, secondary, and exploratory objectives of the study are as follows:

Primary:

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

The primary endpoint will be analyzed at 48 hours post-baseline (Follow-up 1) by CKD stage III and stage IV independently in addition to the collective stage III/IV group analyses.

Secondary:

- To demonstrate the safety of i.v. iodinated iso-osmolar iodixanol (Visipaque™ Injection 320 mgI/mL) usage in CECT for CKD stage III/IV patients by evaluating the incidence of AKI stage ≥ 2 , per AKIN SCr criteria [AKIN 2015] [Mehta et al. 2007], in patients undergoing CECT with iodixanol vs patients receiving placebo and undergoing NECT and an additional non-contrast-enhanced ultrasound imaging modality.
- To demonstrate the safety of i.v. iodinated iso-osmolar iodixanol (Visipaque™ Injection 320 mgI/mL) usage in CECT for CKD stage III/IV patients by evaluating the incidence of AKI by other definitions (standard definition of contrast induced nephropathy (CIN) [Mehran and Nikolsky 2006], and AKI stages ≥ 2 by Waikar criteria [Waikar and Bonventre 2009]) in patients undergoing CECT with iodixanol vs patients receiving placebo and undergoing NECT and an additional non-contrast-enhanced ultrasound imaging modality.
- To demonstrate the safety of i.v. iodinated iso-osmolar iodixanol (Visipaque™ Injection 320 mgI/mL) usage in CECT for CKD stage III/IV patients by evaluating mortality and morbidity within 6 months of intervention in patients undergoing CECT with iodixanol vs patients receiving placebo and undergoing NECT and an additional non-contrast-enhanced ultrasound imaging modality.
- To assess image quality/diagnostic confidence of CECT and NECT plus Ultrasound.

Exploratory:

- [REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]

6 STUDY DESIGN

6.1 Overall Study Design and Plan

This parallel-group, randomized, placebo-controlled study will examine the incidence and severity of AKI in patients with CKD stage III/IV following an i.v. injection of iso-osmolar iodinated contrast material iodixanol (Visipaque Injection 320 mgI/mL), as compared with patients who did not receive contrast medium during their scheduled post-EVAR surveillance imaging. The patient population under investigation in this study is defined as outpatients who have undergone a successful EVAR procedure, have already undergone an imaging assessment at 1 month after the EVAR procedure and for whom a post-EVAR surveillance examination is due. A total of 1164 patients are planned to be randomized at approximately 80 centers located in the United States of America, Canada, and Europe.

The patients will be randomly assigned in a 1:1 ratio to undergo either CECT or NECT for this routine surveillance CT examination (full details are provided in the CT Imaging Manual). Patients in the CECT arm will receive a 100-mL i.v. injection of iodixanol (Visipaque Injection 320 mg I/mL), followed by a 10 mL saline flush, for enhancement of the CT examination. Patients in the NECT arm will receive a volume-matched i.v. injection of a saline placebo, followed by a 10 mL saline flush, before their CT examination. All patients (CECT and NECT arms) will be required to drink 500 mL of fluids following collection of blood samples for central analysis of SCr and prior to scanning. All patients (CECT and NECT arm) will be required to drink at least 2500 mL of fluids in the 24 hours immediately following CT scanning. To ensure a consistent approach, oral hydration is preferred, however, in case of concern about the patient's compliance and/or capability to follow the oral hydration instructions, i.v. administration of isotonic crystalloid solution (saline or bicarbonate) may be considered. In case of i.v. administration of crystalloids, the combination of oral and i.v. fluids must equal a minimum of 500 mL pre-contrast material administration and 2500 mL within 24 hours post-contrast material administration. Subjects will be asked to record their fluid intake. The volume of fluids, before and within 24 hours after administration, must be carefully documented in source records and in the CRF. Decision on use of i.v. hydration will be made and documented before randomization and implemented regardless of whether the subject is randomized to the NECT or CECT arm. The use of *N*-acetylcysteine (NAC) is discouraged for the purpose of preventing AKI.

To fulfil the ethical requirement for clinical equipoise, the patients in the NECT arm will undergo non-contrast duplex ultrasonography after their NECT imaging; ideally on the same day as the NECT imaging and within 2 days of performing the NECT. The purpose of the duplex ultrasonography is to detect vascular complications (e.g., endoleaks) that may not be visible in NECT images.

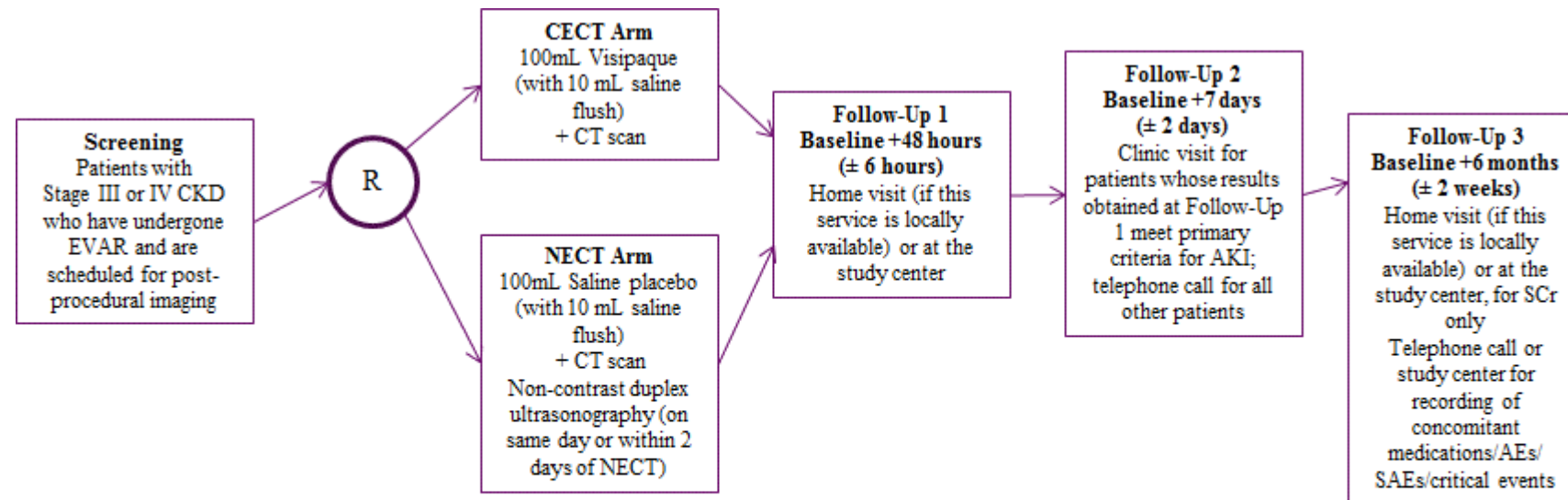
Images will be read at the site according to usual clinical practice to facilitate patient management decisions. The images obtained from the patients in both study arms will also be read in a central independent blinded read to assess imaging quality/diagnostic confidence.

Follow-ups will occur at 48 hours, 7 days, and 6 months post-baseline. At Follow-up 1 (48 hours \pm 6 hours), blood samples will be collected either at the patient's home (if this service is locally available) or at the study center and concomitant medications, adverse events (AEs), serious adverse events (SAEs) and critical events recorded (by telephone if the patient receives a home visit). If Nephrocheck® biomarker analysis will be performed, urine samples will be collected. Follow-up 2 (7 days \pm 2 days) will be a clinic visit for those patients who meet primary criteria (AKI stage \geq 1, per AKIN) at Follow-up 1 and a telephone follow-up for all other patients. If the patient attends the clinic, blood samples for clinical chemistry will be collected and concomitant medication, vital signs, physical examination, AEs, SAEs and critical events will be recorded. If the patient receives a telephone follow-up, concomitant medication, AEs, SAEs and critical events will be recorded. At Follow-up 3 (6 months \pm 2 weeks), a blood sample for SCr will be collected either at the patient's home (if this service is locally available) or at the study center and concomitant medications, AEs, SAEs and critical events will be recorded (by telephone for patients receiving a home visit).

Study critical events will be adjudicated by a Critical Events Adjudication Committee (CEAC; Section 9.7). A Data Safety Monitoring Board (DSMB) will review and evaluate safety data periodically throughout the study (Section 9.8).

An overview of the study design is presented in [Figure 1](#).

A subset of patients (no more than 100), at selected sites in the USA, may also receive the inert fluorescent agent MB-102 (manufactured by MediBeacon, Saint Louis, MO, USA) and will be monitored by ORFM (Sections 8.1.3 and 9.2.3).

Figure 1 Study Diagram

AKI = Acute kidney injury
 CECT = Contrast-enhanced computed tomography
 CKD = Chronic kidney disease
 EVAR = Endovascular aneurysm repair
 NECT = Non-enhanced computed tomography
 R = Randomization

6.2 Study Timeframe

Patient recruitment is planned to start in the first half of 2017.

The expected duration of the study is approximately 2 years.

The end of the study is defined as the date of the last visit of the last subject in the study.

6.3 Risks and Benefits to Patients

The potential risks for approved iodinated contrast agents are well known and have been detailed in American College of Radiology's Manual on Contrast Media [\[ACR 2015\]](#). The majority of AEs related to contrast media are mild or moderate, non-life-threatening events. Serious acute contrast reactions are rare and have historically occurred in approximately 1 or 2 per 10,000 (0.01% to 0.02%) intravascular injections of low-osmolar contrast media [\[Katayama et al 1990\]](#). Visipaque™ was approved in 1992 and has since been used in more than 115 million patients. In this phase 4 trial, Visipaque™ will be used in line with approved product information and the risks are also clearly described in the Investigator's Brochure (IB).

Potential risks to patients enrolling into this study are believed to be similar to those described in the IB because: 1) Visipaque™ is approved for and has been routinely used in a similar population of patients in current clinical practice, and no particular safety concern has been noted for the patient population to be included (see IB/RSI for details); 2) the dose of Visipaque™ that will be administered is within the dosing range specified in the IB, which should reduce the risk of unexpected AEs.

The patients who participate in this study are patients who would be receiving a CT examination as part of their standard care therefore participation in the study provides similar risks and benefits to participants as those managed according to routine clinical practice. Participation in this study will not increase patients' lifetime exposure to imaging radiation.

There is no universally accepted imaging protocol for post-EVAR surveillance (e.g., for detection of endoleaks, detection of mechanical changes in the stent-graft, and evidence of expansion or shrinkage of the residual sac). The American College of Radiology notes that computed tomography angiography (CTA) is considered the gold standard for the diagnosis of endoleaks [\[ACR 2012\]](#). In 2010, the Society of Interventional Radiology published clinical practice guidelines for EVAR [\[Walker et al 2010\]](#). These guidelines, which were endorsed by the Cardiovascular and Interventional Radiological Society of Europe and the Canadian Interventional Radiology Association, indicated that even though CTA is the most commonly used examination for post-EVAR surveillance, unenhanced CT, magnetic resonance angiography, ultrasonography, and even simple radiography, remain commonly used and appropriate. The recent ESC 2014 Guideline on the diagnosis and treatment of aortic diseases is also largely in line with guidelines published earlier in terms of imaging follow-up recommendations, and the use of color-Doppler US can be considered as an alternative in case neither endoleak nor abdominal aortic aneurysm sac enlargement was documented during the first year after EVAR [\[ESC Guidelines 2014\]](#). In practice, vascular surgeons do not always

follow these guidelines; and if the results of the first post-EVAR CTA are negative, unenhanced CT or ultrasonographic exams are often ordered instead of CTA for continued surveillance. Thus, after the first post-EVAR examination, there is clinical equipoise between imaging methods that do and do not require administration of contrast medium. As a result, it is ethically acceptable to use randomization to assign some patients to receive contrast medium and some patients to be evaluated without the use of contrast medium.

This study's safety monitoring plan is justifiable and adequate from a safety standpoint in view of the following:

- The design of the safety plan permits a comparison of the safety response to Visipaque™ 320mg I/mL Injection compared to placebo (including non-contrast duplex ultrasonography) under baseline and post-investigational medicinal product (IMP) administration conditions.
- The 6-month safety monitoring follow-up permits the evaluation of late-appearing significant adverse effects that may emerge or progress after the administration of Visipaque™ 320mg I/mL Injection compared to placebo.
- The measures used to assess safety are well-defined and reliable, and the proposed safety analyses are adequate to assess the effects of the administration of Visipaque™ Injection 320 mg I/mL compared to placebo.

7 SELECTION AND WITHDRAWAL OF PATIENTS

7.1 Patient Selection

Patients will have undergone a successful EVAR and will have been scheduled for post-procedural imaging surveillance with CT at a participating center.

7.2 Inclusion Criteria

Patients may be included in the study if they meet all of the following criteria:

- (1) Is ≥ 18 years of age at the time that written informed consent is obtained.
- (2) Is male or is a non-pregnant, non-lactating female who is either surgically sterile (has a documented bilateral tubal ligation or oophorectomy and/or documented hysterectomy) or is postmenopausal (cessation of menses for more than 1 year). Women of childbearing potential must use adequate contraception* from Screening until 30 days after the Baseline Visit and must have a negative result for a urine human chorionic gonadotropin pregnancy test at the Baseline Visit.
- (3) Is an outpatient who has undergone successful EVAR and is scheduled for his/her next post-procedural imaging follow-up examination.
- (4) Has previously completed one or more of his or her post-EVAR surveillance imaging examination(s) that provided evidence on stable post-EVAR status.
- (5) Has a documented diagnosis of stage III or IV (defined as $30 \leq \text{estimated glomerular filtration rate (eGFR)} < 60 \text{ mL/min/1.73 m}^2$ and $15 \leq \text{eGFR} < 30 \text{ mL/min/1.73 m}^2$, respectively, according to the Modification of Diet in Renal Disease [MDRD] equation) CKD and stable renal function (last 2 SCr values within $\pm 0.5 \text{ mg/dL}$ of each other, with the most recent value within 14 days prior to the scheduled CT examination and the preceding value within 1 to 12 months before that).
- (6) Is able to provide written informed consent.
- (7) Is able and willing to comply with all study procedures as described in the protocol.

* Adequate contraception is based on those methods identified in the Clinical Trial Facilitation Group (CTFG) document [\[CTFG Guidance 2014\]](#) for clarification of effective contraception. Such methods include: combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal); progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable); intrauterine device; intrauterine hormone-releasing system; bilateral tubal occlusion; vasectomized partner; sexual abstinence, progestogen-only oral hormonal contraception, where inhibition of ovulation is not the

primary mode of action, male or female condom with or without spermicide cap, diaphragm or sponge with spermicide (refer to Section 8.6).

7.3 Exclusion Criteria

Patients must be excluded from participating in this study if they meet any of the following criteria:

- (1) Is pregnant, lactating, is possibly pregnant, or is actively trying to conceive during the study period.
- (2) Is a patient for whom an endoleak or other clinically meaningful EVAR-related complication (as judged by the investigator) has already been discovered.
- (3) Is a patient who is undergoing surveillance following a Thoracic Endovascular Repair (TEVAR).
- (4) Has a known or suspected history of immediate or delayed hypersensitivity (including but not limited to hives, anaphylactoid or cardiovascular reactions, laryngeal edema, and bronchospasm) to iodine or any iodinated contrast medium.
- (5) Is using metformin (e.g., Glucophage®) that cannot be discontinued for the period of 48 hours prior to the Baseline Visit and for at least 48 hours after the imaging procedure (renal function must be evaluated before metformin is resumed).
- (6) Has been exposed to any intravascular iodinated contrast medium in the 14 days prior to the Baseline Visit.
- (7) Has congestive heart failure (New York Heart Association [NYHA] Class IV) or hepatic failure/liver cirrhosis according to the investigator's judgement.
- (8) Has stage V CKD, defined as eGFR <15 mL/min/1.73 m² according to the MDRD equation.
- (9) Has a pre-existing requirement for renal dialysis.
- (10) Has undergone percutaneous transluminal renal angioplasty (PTRA) within 12 months before the index EVAR procedure or is scheduled to undergo PTRA during the study period.
- (11) Has any clinically active, serious, life-threatening disease, medical, or significant psychiatric condition; has a life expectancy of less than 6 months; or is, in the Investigator's opinion, unsuitable for participation in the study for any reason.
- (12) Has been enrolled in another clinical study within the 30 days prior to the Screening Visit or is planned to enroll in another clinical study within the duration of this study.

- (13) Has been previously enrolled in this study.
- (14) Is using i.v. vasopressor or inotropic medications.
- (15) Has used nonsteroidal anti-inflammatory drugs (NSAIDs) or any nephrotoxic medication within 48 hours of the Baseline Visit or will do so within 72 hours after the CT procedure (renal function must be evaluated before any nephrotoxic medication is resumed) – with the exception of acetylsalicylic acid (Aspirin) at a dose of ≤ 100 mg daily (QD).
- (16) Has been hospitalized within 30 days prior to Screening Visit for any reason other than practical purposes for management of tests or diagnostic assessments.

7.4 Withdrawal and Termination Criteria

7.4.1 Patient Withdrawal

There are no formal withdrawal criteria for this study. During the conduct of the study, the Sponsor will review the safety data for trends and signals that would indicate the need for withdrawal of a patient.

In accordance with the Declaration of Helsinki, each patient is free to withdraw from the study at any time. Investigator(s) also have the right to withdraw patients from the study in the event of illness, AEs, or other reasons concerning the health or well-being of the patient, or in the case of lack of co-operation.

Should a patient decide to withdraw after administration of Visipaque™ 320 mg I/mL Injection or saline placebo, or should the Investigator(s) decide to withdraw the patient, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation at the time of the patient's withdrawal should be made and an explanation given of why the patient is withdrawing or being withdrawn from the study.

The reason for withdrawal must be noted in the electronic Case Report Form (eCRF). If the reason for withdrawal is a clinical AE, monitoring will continue until the outcome is evident. The specific event or test result(s) must be recorded in the eCRF.

7.4.2 Study or Site Termination

The Sponsor reserves the right to terminate the study at any time. The Sponsor also reserves the right to discontinue participation of a study center at which no patients have been enrolled within 6 months of initiation or in case of safety concerns or major protocol violations.

8 TREATMENT OF PATIENTS

8.1 Investigational Medicinal Product (IMP)

8.1.1 Visipaque™ Injection

Visipaque™ (iodixanol) Injection 320 mg I/mL will be used as the contrast agent for the CECT (CTA) examinations performed in this study.

Visipaque™ Injection 320 mg I/mL is provided as a clear, colorless to pale yellow aqueous solution under secure conditions and must not be frozen. The product must be stored protected from light and must be kept at room temperature, between 15°C to 30°C [59°F to 86°F]. Visipaque™ Injection 320 mg I/mL should not be refrigerated.

Visipaque™ Injection 320 mg I/mL will be supplied in 100-mL bottle containers. An “investigational use only” label will be attached to the individual containers and the supply box.

Patients will be dosed with 100 mL Visipaque™ Injection 320 mg I/mL followed by a 10 mL saline flush to ensure delivery of the full dose of Visipaque in accordance with the protocol and the CT Imaging Manual.

8.1.2 Comparator (Placebo)

The placebo will consist of 100 mL saline to be administered in a single i.v. injection followed by a 10 mL saline flush. The saline will be provided by a central supplier and stored securely at room temperature.

Further details on administration of saline placebo are given in the CT Imaging Manual.

8.1.3 Optical Renal Function Monitoring

A subset of patients (no more than 100), at selected sites in the USA, may also receive an inert fluorescent pyrazine-based tracer agent (MB-102), which is used with an ORFM to enable accurate tracking of kidney function, by non-invasively measuring fluorescent light emission over time. This will be the purpose of a specific amendment to this protocol during the course of the present clinical trial.

MB-102 will be provided directly from MediBeacon (MediBeacon, Saint Louis, MO, USA) and will be administered at the Baseline Visit, 1 hour prior to Visipaque™ or saline placebo.

Further information regarding MB-102 and ORFM will be provided to the participating study centers as a separate local amendment to this protocol. Specific patient information will be

provided to potential patients and their consent to participate will be documented on an IRB approved Informed Consent Form.

8.1.4 IMP Accountability

Each Investigator is responsible for ensuring that deliveries of Visipaque™, saline placebo and other study materials from the Sponsor are correctly received, recorded, handled, and stored safely and properly in accordance with all applicable regulatory guidelines, and used in accordance with this protocol.

All Visipaque™ and placebo containers (opened, unopened, or empty) must be returned to the Sponsor or destroyed on site after the study and overall drug accountability have been completed by the Sponsor or representative. A list of Visipaque™, placebo and other materials that were returned, or destroyed, must be prepared and signed by the Principal Investigator or designee. If there are any discrepancies, an explanation for these should also be provided.

8.1.5 Registration of Investigational Medicinal Product(s) Complaints

In the event of an IMP complaint (e.g., breakage, leakage, particulate matter, discoloration), the Investigator or recipient of the IMP is requested to report the problem on the relevant shipping documentation (e.g., 'Delivery Note for Product', Drug Shipping and Receiving Form, or equivalent form). This should be promptly forwarded to the person indicated on the shipping documentation. Once received, the Clinical Supplies Manager will register the complaint and determine if the complaint is minor or significant according to Sponsor procedures. All complaints will be followed up and the appropriate action will be implemented according to Sponsor procedures.

8.2 Method of Numbering Patients and Assigning Patients to Treatment Groups

A unique allocation number will be assigned to each patient at a center in successive order of entering the study after signing the informed consent form. No patient may be entered or screened (after failing to meet inclusion/exclusion criteria) into the study more than once. The allocation number will be unique for each patient in the study and will consist of 7 numbers in total: 3 numbers for the center identification and 4 numbers for the patient identification at the center (e.g., 002-0001: first patient in center No. 2).

Once a patient number is assigned, it cannot be reassigned even if the patient is deemed ineligible or withdraws consent. To preserve the scientific integrity of the study, numbers must be assigned in numeric order.

A patient who has given informed consent (or for whom informed consent has been given) but does not fulfil the criteria to participate in the study will receive a patient number and will be logged as a screening failure within the interactive web response system (IWRS)/ interactive

voice response system (IVRS). The patient will also be documented on the Screening Log by using the patient's initials and patient number.

Once patients have completed the screening process they will be enrolled in the study and will be randomly assigned to the NECT group or the CECT group in a 1:1 ratio in accordance with a pre-specified randomization list. Allocation to the enrolment groups, including randomization, will be performed centrally (via the IWRS or IVRS) by the Sponsor or contract research organization (CRO). Randomization will be stratified by CKD stage to achieve a balance of this factor between treatment groups.

No patient will be administered Visipaque™ or saline placebo before it has been determined that the patient meets the study's inclusion/exclusion criteria and signed and dated informed consent has been obtained.

8.3 Selection of Doses and Timing

Patients randomized to receive Visipaque™ will be dosed with 100 mL Visipaque™ Injection 320 mg I/mL followed by a 10 mL saline flush. The size of the saline placebo dose is intended to mimic the size of the Visipaque™ dose, i.e., 100 mL saline followed by 10 mL saline flush.

The dose of Visipaque™ or saline placebo will be administered prior to the CT procedure as detailed in the Imaging Manual.

8.4 Blinding

This study is not blinded.

8.5 Prior and Concurrent Medications or Procedures

Any medications taken by the patient, medical procedure, or diagnostic assessment within 14 days before Visipaque™ or saline placebo administration and up to the end of Follow-Up 3 will be recorded in the eCRF along with the indication for use and dosage. Either the generic or the trade name may be recorded. The Sponsor/CRO will encode all therapy and medication according to a current well-recognized dictionary of medical codes.

Metformin, NSAIDs, and drugs with nephrotoxic potential will be required to be discontinued temporarily per exclusion criteria #5 and #15, and the current use of i.v. vasopressor or inotropic medications is prohibited per exclusion criterion #14. The prophylactic use of acetylsalicylic acid (Aspirin) in a dose of ≤ 100 mg QD is permitted. The use of *N*-acetylcysteine (NAC) is discouraged for the purpose of preventing AKI.

8.6 Contraception and Pregnancy Avoidance Procedure

Women of childbearing potential who are sexually active with a non-sterilized male partner and males who are sexually active with a partner of childbearing potential must use adequate contraception from Screening until 30 days after the Baseline Visit. A woman NOT of childbearing potential is defined as surgically sterile (has a documented bilateral tubal ligation or oophorectomy and/or documented hysterectomy) or postmenopausal (cessation of menses for more than 1 year).

Acceptable methods of contraception that are considered as highly effective are defined as those with no higher than a 1% failure rate based on those methods identified in the CTFG document for clarification of effective contraception [CTFG Guidance 2014]. Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation¹:
 - oral
 - intravaginal
 - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation¹:
 - oral
 - injectable
 - implantable²
- intrauterine device²
- intrauterine hormone-releasing system²
- bilateral tubal occlusion²
- vasectomized partner^{2,3}

¹ Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.

² Contraception methods that in the context of CTFG guidance are considered to have low user dependency.

³ Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success.

- sexual abstinence⁴

Acceptable, but not highly effective, birth control methods that result in a failure rate of more than 1% per year include:

- progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- male or female condom with or without spermicide⁵
- cap, diaphragm or sponge with spermicide⁵

Patients will be provided with information on acceptable methods of contraception as part of the subject informed consent process. Women of childbearing potential must have a negative result for a urine human chorionic gonadotropin pregnancy test at the Baseline Visit.

8.7 Treatment Compliance

Patients will receive Visipaque™ 320 mgI/mL or saline placebo under direct supervision of study personnel. Each administration volume will be checked and the vial code and volume per administration, date and time will be recorded in each patient's eCRF. Doses administered outside of specific dose requirements or defined range must be reported as protocol deviations (see Section 13.3).

⁴ In the context of CTFG guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

⁵ A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods

9 STUDY PROCEDURES

All efficacy and safety measurements obtained during the course of the study are summarized in the Study Schedule of Events ([Table 1](#)).

Table 1 Study Schedule of Events

Parameter	Screening Visit (within -14 days) ^a	Baseline Visit			Follow-Up 1 (Baseline +48 hours ±6 hours) ^d	Follow-Up 2 (Baseline +7 days ±2 days) ^c	Follow-Up 3 (Baseline + 6 months ±2 weeks) ^d
		Pre-Scan ^a	Scan	Post Scan ^b			
Informed consent signed	X						
Inclusion/exclusion criteria	X ^a	X ^a					
Demographic information	X						
Medical/surgical history	X ^a	X ^a					
Prior/concomitant medication or procedures	X ^a	X ^a			X	X	X
Physical examination	X ^a	X ^a				X ^c	
Electrocardiogram (12-lead)	X						
Vital signs ^e	X ^a	X ^a		X	X	X ^c	
Pregnancy test (if indicated) ^f	X ^a	X ^a					
Randomization to CECT or NECT arm		X					
Blood and urine sampling for screening SCr, clinical chemistry, hematology, TSH (local laboratory) ^g	X						
Blood sampling for SCr, cystatin C, and N-GAL (central laboratory) ^g		X			X	X ^c	X ^d
Urine sampling for NephroCheck® biomarkers (local laboratory, if available) ^g		X		X	X		
Adverse events	X	X		X	X	X	X
Serious adverse events and critical events as per CEAC ^h	X	X		X	X	X	X ^d
Hydration (500 mL) ⁱ		X					
ORFM (selected sites only)		X		X			
Saline administration (NECT arm only)			X				
Visipaque™ injection 320 mgI/mL administration (CECT arm only)			X				
CT scan ^j			X				
Non-contrast duplex ultrasonography (NECT arm only) ^k				X			
Reminder re: hydration (2500 mL) ⁱ				X			
Record hydration volume		X		X	X		

Table 1 Study Schedule of Events

Parameter	Screening Visit (within -14 days) ^a	Baseline Visit			Follow-Up 1 (Baseline +48 hours ±6 hours) ^d	Follow-Up 2 (Baseline +7 days ±2 days) ^e	Follow-Up 3 (Baseline + 6 months ±2 weeks) ^d
		Pre-Scan ^a	Scan	Post Scan ^b			

CEAC = Critical Events Adjudication Committee; CECT = contrast-enhanced computed tomography; NECT = nonenhanced computed tomography; ORFM = optical renal function monitor; SCr = serum creatinine; TSH = Thyroid-stimulating hormone

^a Screening procedures may be conducted on the same day as baseline pre-scan assessments, dependent on the site's local laboratory turnaround time for SCr. **In this instance assessments required for screening and baseline pre-scan need only be conducted once. If the screening and baseline assessments occur on separate days, the assessments need to be completed at each visit.** A signed consent must be obtained from 14 days prior to the Baseline Visit and before any study screening or pre-scan assessments are conducted.

^b Within 4 hours after scanning.

^c If results obtained at Follow-Up 1 meet primary criteria (AKI stage ≥ 1 , per AKIN), Follow-Up 2 will be performed as a clinic visit. A telephone follow-up will be performed for all other patients. If the patient attends the clinic, the following will be performed: concomitant medication will be recorded, vital signs will be recorded, blood samples for clinical chemistry will be collected, physical examination, adverse events and critical events will be recorded. If the patient receives a telephone follow-up, the following will be recorded: concomitant medication, adverse events and critical events.

^d A blood sample for SCr will be collected either at the patient's home (if this service is locally available) or at the study center, and SAEs and critical events will be recorded either by telephone (for patients receiving a home visit) or at the study center.

^e Vital signs are to be measured in the sitting position. The patient should rest for at least 5 minutes before vital signs measurement.

^f If applicable, a negative urine pregnancy test must be obtained at the Screening and Baseline Visit for female patients.

^g All blood samples taken prior to dosing and following the scan will be taken from venous blood. Local laboratories will be used for determination of eligibility for the trial and for stratification during randomization. A central laboratory will be utilized for analysis of SCr, cystatin C, and N-GAL collected at the Baseline Visit, Follow-Up 1 and Follow-Up 2 (for patients meeting primary AKIN criteria at Follow-Up 1). Sampling for Follow-Up 1 should occur as close to 48 hours as possible to support the primary endpoint assessment for AKI [ACR 2015], with use of the -6 hour window being preferable to use of the +6 hour window. Urine samples collected for NephroCheck® biomarkers (TIMP-2 and IGFBP-7) for patients where local NephroCheck® testing is available will be taken just before the scan, 4 hours post scan, and at 48 hours post scan.

^h Critical events, including EVAR-related post-baseline events, will be collected from administration to approximately 6 months after administration of Visipaque™ Injection/ saline placebo for assessment by the CEAC.

ⁱ 500 mL of fluids after SCr sampling and before the CT scan to be consumed. 2500 mL of fluids within the 24 hours post-CT period to be consumed. In case of concern about the patient's compliance and/or capability to follow the oral hydration instructions, i.v. administration of isotonic crystalloid solution (saline or bicarbonate) may be considered. Decision on use of i.v. hydration to be made and documented prior to randomization and performed regardless of whether the patient is randomized to the NECT or CECT arm.

^j CT scan according to correct acquisition protocol.

^k Non-contrast duplex ultrasonography will be performed ideally on the same day as NECT imaging and within 2 days of performing the NECT according to correct acquisition protocol.

9.1 Screening Visit

A Screening visit will take place up to 14 days before a scheduled CT examination for post-EVAR surveillance. Note that screening visit assessments may be conducted on the same day as baseline pre-scan assessments, dependent on the site's local laboratory turnaround time for SCr. In this instance assessments required for screening and baseline pre-scan need only be conducted once. If the screening and baseline assessments occur on separate days, the assessments need to be completed at each visit.

At the Screening visit, the following will be collected and/or performed:

- Written informed consent. *Note, the consent process may start prior to the Screening visit but the most current version of the consent form must be signed within 14 days prior to the baseline visit and prior to any screening assessments being conducted.*
- Demographic information.
- General medical/surgical history.
- Prior and concomitant medications.
- All female patients of child-bearing potential will undergo a urine pregnancy test.
- Physical examination.
- Vital signs (blood pressure, heart rate, respiration rate) in the sitting position.
- 12-lead electrocardiogram (ECG).
- Blood samples for SCr measurement. Samples will be tested locally for the purposes of checking eligibility and assigning CKD stage.
- Blood samples for local laboratory evaluation (clinical chemistry and hematology); see [Table 2](#).
- Urine samples for local laboratory evaluation; see [Table 2](#).
- Pre-treatment AEs and SAEs (from time of signing informed consent).

Patients must satisfy all the inclusion criteria and none of the exclusion criteria listed in Sections [7.2](#) and [7.3](#) and must provide signed and dated informed consent prior to entering the study. Patients who will undergo ORFM will provide specific written informed consent to undergo the procedure as part of the Screening Visit at the selected study centers in the USA.

Each patient who is enrolled in the study will be assigned a unique study number, as described in Section [8.2](#).

Waivers or protocol exceptions will not be granted prospectively by the Sponsor under any circumstances. Any exceptions to protocol specified requirements will be considered as protocol deviations.

All screening procedures should be completed prior to randomization of the patient.

9.2 Baseline Visit

The Baseline visit will take place within 14 days of the Screening visit.

At the Baseline Visit, the following will be collected and/or performed:

Before administration of Visipaque™ 320 mgI/mL or saline placebo the following will be collected and/or performed:

- All female patients of child-bearing potential will undergo a urine pregnancy test.
- Inclusion/exclusion criteria will be checked.
- General medical/surgical history.
- Prior and concomitant medication.
- Physical examination.
- Vital signs (blood pressure, heart rate, respiration rate) in the sitting position.
- The patient will be randomized to the CECT arm or NECT arm by IWRS/IVRS.
- Blood samples will be drawn for laboratory evaluation (local clinical chemistry and hematology if not already done at screening and for central determination of SCr, cystatin C and N-GAL); see [Table 2](#).
- Urine sample for clinical chemistry (if not already done at screening), and Nephrocheck® biomarkers (where local NephroCheck® testing is available).
- The patient will receive oral hydration (500 mL of fluids) following collection of blood samples for central analysis of SCr. In case of concern about the patient's compliance and/or capability to follow the oral hydration instructions, i.v. administration of isotonic crystalloid solution (saline or bicarbonate) may be considered. Decision on use of i.v. hydration will be made and documented before randomization (to be implemented regardless of whether the subject is randomized to the NECT or CECT arm).
- Pre-treatment AEs, SAEs and critical events, including EVAR-related post-baseline events (from time of signing informed consent).

- Optional ORFM; for a subset of patients at selected sites, MB-102 will be administered 1 hour prior to Visipaque™ or saline placebo.

Administration of Visipaque™ 320 mgI/mL or saline placebo:

- Patients in the CECT arm will receive 100 mL of Visipaque™ Injection 320 mg I/mL followed by a 10 mL saline flush.
- Patients in the NECT arm will receive 100 mL of saline placebo, followed by a 10 mL saline flush.
- Study personnel must remain vigilant for the occurrence of AEs, particularly those that may be life-threatening. Personnel who are 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.

After administration of Visipaque™ 320 mgI/mL or saline placebo the following will be collected and/or performed:

- All patients will undergo a CT scan.
- Patients in the NECT arm will undergo non-contrast duplex ultrasonography after their nonenhanced CT scan, ideally on the same day as the NECT imaging and within 2 days of performing the NECT.
- Vital signs (blood pressure, heart rate, respiration rate) in the sitting position.
- All patients will need to drink at least 2500 mL of fluids in the 24 hours immediately following the CT scan. Patients in the NECT arm should start drinking the fluids after their ultrasonography, if it is performed on the same day as the NECT. In case of concern about the patient's compliance and/or capability to follow the oral hydration instructions, i.v. administration of isotonic crystalloid solution (saline or bicarbonate) may be considered. The total volume of fluid intake, in-clinic, will be documented.
- Treatment-emergent AEs, treatment-emergent SAEs and critical events, including EVAR-related post-baseline events.
- Urine samples for Nephrocheck® biomarkers (where local NephroCheck® testing is available) collected 4 hours post-CT.
- Optional ORFM; for a subset of patients at selected sites in the USA, monitoring of renal function will continue up to 4 hours post-CT.
- On discharge, patients will be instructed to continue with fluid consumption to ensure a total of 2500 mL over the 24 hours following the CT scan (NECT and CECT arms). Patients will be provided a card to document fluid consumption.

See Section 10.2 and the Study Schedule of Events Table (Table 1) for further details.

9.2.1 Image Acquisition

Contrast-enhanced and nonenhanced CT images will be acquired in accordance with the CT Imaging Manual. The appropriate study personnel shall deliver the dose of Visipaque™ 320 mg I/mL or the saline placebo dose. The entire contents of the 100 mL of Visipaque™ 320 mg I/mL or saline placebo should be administered and followed by a 10 mL saline flush. The administration should be timed properly in accordance with the Imaging Manual to provide an optimal arterial and delayed venous phase following the nonenhanced phase.

All CECT image sets from the treatment group and NECT image sets from the placebo group will be sent to the Sponsor in DICOM format. These image sets will also be archived at the clinical site in accordance with the CT Imaging Manual.

9.2.2 Duplex Ultrasonography Imaging

Non-contrast duplex ultrasonography images will be acquired according to the Ultrasound Imaging Manual. All study duplex ultrasound image sets will be sent to the Sponsor. These image sets will also be archived in accordance with the Ultrasound Imaging Manual.

9.2.3 Optical Renal Function Monitoring

A United States-based company, MediBeacon (Saint Louis, MO), has developed an inert fluorescent pyrazine-based tracer agent (MB-102), which is used with an ORFM to enable accurate tracking of kidney function, by non-invasively measuring fluorescent light emission over time. A sensor connected to the ORFM is attached to the patient's skin and the tracer agent is then injected intravenously, after which the ORFM starts to record the patient's GFR in real time. The tracer agent is inert and completely excreted via the kidneys; it has no systemic effects, no protein-binding occurs and no metabolites are produced.

A subset of patients (no more than 100), at selected sites in the USA, may be recruited in order to investigate this exploratory endpoint. MB-102 will be administered at the Baseline visit, 1 hour prior to Visipaque or saline placebo, and monitoring of renal function will continue up to 4 hours post-CT. This will be the purpose of a specific amendment to this protocol during the course of the present clinical trial.

Further information regarding MB-102 and ORFM will be provided to the participating study centers as a separate local amendment to this protocol. Specific patient information will be provided to potential patients and their consent to participate will be documented on an IRB approved Informed Consent Form.

9.3 Follow-Up 1

Follow-up 1 will be scheduled for 48 hours \pm 6 hours after the Baseline Visit. Blood and urine samples will be collected either at the patient's home (if this service is available locally) or at the study center. The following will be collected:

- Vital signs (blood pressure, heart rate, respiration rate) in the sitting position.
- Blood sample for SCr, cystatin C, N-GAL. Sampling for Follow-Up 1 should occur as close to 48 hours as possible to support the primary endpoint assessment for AKI [ACR 2015], with use of the -6 hour window being preferable to use of the +6 hour window.
- Urine sample for Nephrocheck® biomarkers (where local NephroCheck® testing is available).
- Concomitant medication, AEs, SAEs and critical events including EVAR-related post-baseline events (collected by telephone call for patients receiving a home visit).
- Collect patient card with fluid hydration volumes and check accuracy with the patient.

See Section 10.2 and the Study Schedule of Events Table (Table 1) for further details.

9.4 Follow-up 2

If the laboratory test results obtained at Follow-up 1 meet primary criteria (AKI stage ≥ 1 , per AKIN), a clinic visit will be scheduled 7 days ± 2 days after the Baseline Visit. All other patients will receive a telephone follow-up at 7 days ± 2 days after the Baseline Visit.

If the patient attends the clinic, the following will be collected and/or performed:

- Concomitant medication.
- Vital signs (blood pressure, heart rate, respiration rate) in the sitting position.
- Blood samples for SCr, cystatin C, and N-GAL (central laboratory analysis).
- Physical examination.
- AEs, SAEs and critical events, including EVAR-related post-baseline events.

If the patient receives a telephone follow-up, the following will be recorded:

- Concomitant medication.
- AEs, SAEs and critical events, including EVAR-related post-baseline events.

See Section 10.2 and the Study Schedule of Events Table (Table 1) for further details.

9.5 Follow-up 3

At 6 months ± 2 weeks after the Baseline Visit, a blood sample for SCr will be collected either at the patient's home (if this service is locally available) or at the study center.

Concomitant medications, AEs, SAEs, and critical events (including EVAR-related post-baseline events) will be recorded either by telephone (for patients receiving a home visit) or at the study center.

See Section 10.2 and the Study Schedule of Events Table (Table 1) for further details.

9.6 Steering Committee

The Steering Committee is responsible for the scientific and technical aspects of the study conduct. It will be comprised of appropriately qualified physicians, independent from the Sponsor. The Steering Committee will advise on the protocol and its amendments. The Steering Committee will promptly review any recommendations made by the DSMB with regards to early termination and/or protocol amendments while remaining blinded to treatment assignments. The Steering Committee will make recommendations that will be communicated promptly to the Sponsor and the reasons for them shall be clearly documented.

The Steering Committee will work according to a charter of rules approved by both the Steering Committee members and the Sponsor.

9.7 Critical Events Adjudication Committee

The CEAC will adjudicate the study critical events (including EVAR-related post-baseline events, as defined and listed in the CEAC charter) in a blinded fashion. It will be comprised of qualified physicians who are experts in the field of nephrology, and other specialties as appropriate, who have relevant experience within clinical trials and are independent from the Sponsor and study centers. The CEAC will be composed of 4 members and governed by a specific CEAC Charter, approved by the CEAC members and the Sponsor. Three members will be required to adjudicate on each critical event and agree on an outcome following review of all available clinical information. The possible outcomes are as follows:

- (1) The event is a study endpoint and there is unanimous agreement on its classification: the event is validated;
- (2) There is unanimous agreement that the event is not a study endpoint;
- (3) More information is required: the CEAC will request more information from the study center via the process defined in the CEAC Charter;
- (4) The event could be a study endpoint, however there is a disagreement on its classification.

In the case that additional information is requested, a second review with the additional information received from the study center will aim to classify the event into the first or second outcome described above.

All cases that cannot be unanimously adjudicated, or where there is a disagreement, will be reviewed in common to obtain a final decision.

Whenever possible, adjudications will be completed remotely using electronic systems that comply with legal and regulatory requirements.

The CEAC decisions will be based on members' blinded reviews of the data provided by Investigators via a CRO. Data provided may include AE, SAE and critical event reports, eCRF downloads, hospital admission/discharge reports and any specific documents requested by a CEAC member. All information will be provided in an anonymized format.

The CEAC will be appointed at the commencement of the study before any patients have been enrolled.

9.8 Data Safety Monitoring Board

An independent DSMB will meet periodically, or as needed, to review and evaluate safety data.

The DSMB will act as an independent committee overseeing all safety aspects of the study, and is comprised of 5 experts with relevant experience in the management of patients and/or safety monitoring in clinical studies. The DSMB members are independent of investigators entering or caring for patients in the study, are independent of the other study committees and are not involved in any other of the study activities than their role in the DSMB. The DSMB may recommend to the Steering Committee and Sponsor termination of the study at any time should prospective ethical or safety guidelines not be met, or propose protocol amendments to ensure safety of study individuals. The DSMB will work according to a Charter approved by DSMB members, the Steering Committee and the Sponsor, which will include (but is not limited to):

- An outline of the study stopping rules, based on SCr, eGFR and events.
- Monitoring of SCr changes measured at 48 hours.
- Events previously adjudicated by the CEAC.

9.9 Image Interpretation

CT and ultrasound images will be read at the site according to usual clinical practice to facilitate patient management decisions.

Images will also be read in a central independent blinded read in order to assess image quality/diagnostic confidence.

Images will be read by a panel of independent blinded readers appropriately qualified in abdominal imaging. Each CECT (CTA) image or NECT image plus duplex ultrasonography image will be read by 3 independent readers who will be randomly selected from the panel.

Detailed reader selection criteria will be provided in the Independent Read Charter. Readers will be provided with a Reader Training Manual for CECT and NECT plus Ultrasound assessments. This manual will provide the detailed assessment criteria which will include, but are not limited to, the diagnosis of the following items with regard to their confidence in making patient management decisions: i.e., status of the graft, stenosis, aneurysm rupture, endoleaks. A 5-point scale will be used to rate the visual assessment of image quality/diagnostic confidence:

5= excellent image quality, highest confidence for use in treatment decisions

4= good image quality, good confidence for use in treatment decisions

3= sufficient image quality, moderate confidence for use in treatment decisions

2= restricted image quality, low confidence for use in treatment decisions

1= poor image quality, no confidence for use in treatment decisions

A rating of 1 or 2 equates to the images being considered non-diagnostic. If a reader gives a 1 or 2 rating, the reader will be required to enter the reason for that rating in a freeform text entry field.

10 EFFICACY, SAFETY, AND OTHER VARIABLES

10.1 Endpoints

10.1.1 Primary Endpoint

Incidence of AKI stage ≥ 1 (AKIN SCr criteria) following an i.v. injection of iodinated iso-osmolar contrast material iodixanol (Visipaque™ Injection 320 mgI/mL) or saline in patients with CKD stage III/IV assessed at 48 hours post-baseline (Follow-up 1).

10.1.2 Secondary Endpoints

AKI Secondary Endpoints:

- Incidence of AKI stage ≥ 2 (by AKIN SCr criteria) following an i.v. injection of iodinated iso-osmolar contrast material iodixanol (Visipaque™ Injection 320 mgI/mL) or saline in patients with CKD stage III/IV assessed at 48 hours post-baseline (Follow-up 1).
- Incidence of AKI (by standard definition of CIN [Mehran and Nikolsky 2006]) following an i.v. injection of iodinated iso-osmolar contrast material iodixanol (Visipaque™ Injection 320 mgI/mL) or saline in patients with CKD stage III/IV assessed at 48 hours post-baseline (Follow-up 1).
- Incidence of AKI stage ≥ 2 (by Waikar criteria [Waikar and Bonventre 2009]) following i.v. administration of iodinated iso-osmolar contrast material iodixanol (Visipaque™ Injection 320 mgI/mL) or saline in patients with CKD stage III/IV assessed at 48 hours post-baseline (Follow-up 1).

Other Secondary Endpoints:

- Mortality and morbidity (i.e. critical events, including EVAR-related post-baseline events, as adjudicated by the CEAC) assessed at 6 months (Follow-up 3) in patients with CKD stage III/IV.
- Blinded independent assessment of image quality/diagnostic confidence using a 5-point scale.

10.1.3 Exploratory Endpoints

- [REDACTED]
- [REDACTED]
- [REDACTED]

10.2 Safety Assessments

The Investigator(s) and the Sponsor/CRO will review the safety data. The following safety data will be collected and evaluated:

- Clinical laboratory parameters: clinical chemistry, hematology, biomarkers and urinalysis ([Table 2](#)).
- Vital signs: systolic/diastolic blood pressure, respiration rate, heart rate.
- 12-lead ECG (screening only).
- Physical examination.
- AEs and SAEs.
- Pre-specified normal limits for vital signs are provided in [Section 15.3](#).

10.2.1 Clinical Laboratory Evaluation

Clinical laboratory parameters assessed in this study are displayed in [Table 2](#). Local laboratories will be used for measuring screening parameters. A central laboratory will be used for analysis of SCr, cystatin C, and N-GAL biomarkers at Baseline, Follow-Up 1, Follow-Up 2 (if a clinic visit takes place), and Follow-Up 3 (SCr only).

Table 2 Clinical Laboratory Parameters

Screening	Baseline	Baseline 4 hours post scan	Follow-Up 1 (48 hours ±6 hours)	Follow-Up 2 (7 days ±2 days)	Follow-Up 3 (6 months ±2 weeks)
<u>Local Laboratory:</u> <u>Clinical Chemistry:</u> Chloride Urea nitrogen Serum creatinine Bicarbonate Sodium Potassium Glucose Alkaline phosphatase Aspartate transaminase Alanine transaminase Bilirubin (Total) Thyroid-stimulating hormone (TSH) ^a <u>Hematology:</u> Hematocrit Hemoglobin Platelet count White blood cell (WBC) count Lymphocyte % <u>Urinalysis (local lab):</u> Glucose Ketone Protein Blood <u>Pregnancy Test:</u> Urine dipstick	<u>Central Laboratory:</u> <u>Clinical Chemistry:</u> Serum creatinine Cystatin C Neutrophil gelatinase-associated lipocalin (N-GAL) <u>Local Laboratory:</u> <u>Urinalysis:</u> NephroCheck® biomarkers (TIMP-2, IGFBP-7) ^b <u>Pregnancy Test:</u> Urine dipstick	<u>Local Laboratory:</u> <u>Urinalysis:</u> NephroCheck® biomarkers (TIMP-2, IGFBP-7) ^b	<u>Central Laboratory:</u> <u>Clinical Chemistry:</u> Serum creatinine Cystatin C N-GAL <u>Local Laboratory:</u> <u>Urinalysis:</u> NephroCheck® biomarkers (TIMP-2, IGFBP-7) ^b	<u>Central Laboratory:</u> <u>Clinical Chemistry:</u> For patients having met the primary AKI criteria: Serum creatinine Cystatin C N-GAL	<u>Central Laboratory:</u> <u>Clinical Chemistry:</u> Serum creatinine

^a supersensitive TSH (sTSH) assay if locally available

^b If local testing is available

The investigator will review laboratory test results to determine the occurrence of clinically important abnormalities which will be reported as AEs. The signed and interpreted laboratory results will be kept together with the patient's eCRF as supplemental pages, both centrally and at the site.

Blood samples will be obtained for assessment of clinical chemistry and hematology at the various pre- and post-treatment time points described in [Table 1](#). Samples will be analyzed at a central laboratory for all samples other than those obtained to confirm eligibility for enrollment (for parameters, see [Table 2](#)). All blood samples will be processed and handled per standard laboratory procedures. Any retained samples will be destroyed at completion of the study.

Urine will be collected at the various pre- and post-treatment time points described in [Table 1](#). Urine voided will be analyzed for the parameters listed in [Table 2](#).

Procedures for obtaining, preparing and shipping blood samples will be detailed in a laboratory manual provided to each study center.

Any abnormal laboratory findings that constitute an AE (e.g., any abnormal findings leading to an intervention other than repeating the laboratory test) should be reported as such and should be followed up until the outcome is known. Also, additional diagnostic tests may be indicated to determine a more precise diagnosis of the patient's condition (e.g., ordering a white blood cell (WBC) differential to help characterize a high or low WBC count, or ordering a determination of red cell indices to help characterize a low hematocrit).

10.2.2 Vital Signs

Before vital signs are measured, the patient should rest for at least 5 minutes (if possible). Vital signs (blood pressure, heart rate, respiratory rate) will be recorded in the sitting position at Screening, Baseline (prior to Visipaque™ or saline placebo administration), and within 1 hour post-administration, at Follow-Up 1 (48 hours post-administration), and at Follow-Up 2 (7 days post-administration; only for patients with AKI stage ≥ 1) according to the study schedule of events ([Table 1](#)). The same, i.e. sitting, position will be used each time vital signs are measured for a given patient and blood pressure will be measured from the arm contralateral to the site of Visipaque or saline placebo administration whenever possible.

10.2.3 ECG

A standard 12-lead ECG will be obtained at Screening or at the latest at Baseline ([Table 1](#)). All ECG recordings will be read at the investigational site prior to the patient being randomized.

Patient management decisions may be based on the 12-lead ECG findings.

10.2.4 Physical Examination

A qualified physician, (or other healthcare professional licensed to perform physical examinations), will conduct physical examinations. The physical examination will include recording an assessment for the presence of abnormalities of the following: general appearance, skin, head, eyes, ears, nose, throat, lungs, cardiovascular system, back and spine, abdomen, extremities, injection site, lymph nodes, and neurological exam.

In the event that *new* abnormal physical findings and *worsening* abnormal physical findings are encountered during the study, these terms are defined as follows: a new abnormal physical finding is defined as one that occurs when a patient's normal baseline physical examination becomes abnormal post baseline; a worsening abnormal physical finding is defined as one that occurs when a patient's abnormal baseline physical examination becomes worse post baseline.

10.2.5 Critical Study Events

Critical events include, but are not limited to:

- Death
- Major Adverse Renal Cardiac Event (MARCE)
- Renal replacement therapy (dialysis, hemofiltration/ultrafiltration, renal transplant)
- Hospitalization due to worsening renal impairment/renal failure
- EVAR-related post-baseline events

Critical events will be identified by the Investigator, documented in the CRF, and adjudicated according to the CEAC Charter.

A critical event is expected to be associated with a reported AE or SAE. More than one critical event may be associated with the same AE or SAE and the terms reported for critical events and AEs/SAEs can differ. Refer to Section [10.2.6](#) for further information.

10.2.6 Adverse Events

Study personnel must remain vigilant for the occurrence of AEs, particularly those that may be life-threatening. Personnel who are 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. Treatment of SAEs should be primarily supportive of vital functions.

AE Definition: An AE is defined as any untoward medical occurrence in a patient or clinical investigation patient who had received an administration of a pharmaceutical product; the occurrence does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of Visipaque™ or saline,

whether or not considered related to that product. Only symptoms/signs that begin or worsen in severity and/or frequency after signing informed consent will be recorded as AEs in the eCRF.

The patients will be closely observed and questioned for any kind of AE during the study procedures and at follow-up appointments throughout the study period with non-leading questioning (e.g., “How do you feel?”). The patients will be instructed to immediately report any symptoms and signs to the study staff (i.e., between formal observations). AEs and SAEs will be recorded from time of signing informed consent until Follow-up 3.

Both the Investigator(s) and Sponsor/CRO will perform a causality assessment on any AE, to assess whether or not there is a reasonable possibility (evidence to suggest) that Visipaque™ or saline caused the event.

Causal relationship

The relationship of an AE with Visipaque™ or saline will be assessed and reported by the investigator as:

- Reasonably related to study drug (“Reasonable cause”): - A causal relationship between Visipaque™ or saline and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.
- Not reasonably related to study drug (“Not reasonable cause”): - A causal relationship between Visipaque™ or saline and an AE is not a reasonable possibility.

A suspected adverse reaction is an AE where reasonable possibility exists for causality between Visipaque™ or saline and the AE.

Expectedness

All Visipaque™-emergent AEs will be assessed, by the Sponsor/CRO, as to whether they were expected to occur or unexpected, meaning not anticipated based on current knowledge found in the applicable safety information included in the IB for Visipaque™.

Unexpected: An unexpected Visipaque™-emergent AE is a reaction, for which the nature, seriousness, severity or outcome is not consistent with the applicable safety information included in the IB.

Expected: An expected Visipaque™-emergent AE is a reaction which is consistent with the applicable safety information included in the IB.

Laboratory AE Evaluation

Interpretation and follow-up of abnormal laboratory test results should be conducted in consideration of the clinical situation of the patient. Any abnormal laboratory findings that constitute an AE should be reported as such and should be followed up until the outcome is known. Also, additional diagnostic tests may be indicated to determine a more precise diagnosis of the patient’s condition (e.g., ordering a WBC differential to help characterize a

high or low WBC count, or ordering a determination of red cell indices to help characterize a low hematocrit).

To ensure a consistent approach, an AE/SAE should always be reported in the CRF for AKI if laboratory test results show a SCr increase of ≥ 0.3 mg/dL (≥ 26.4 $\mu\text{mol/L}$) or an increase to $\geq 150\%$ to 200% (≥ 1.5 to 2.0 fold) from baseline and/or the previous test result.

10.2.7 Serious Adverse Events

An SAE is defined as any AE that:

- Results in death.
- Is life-threatening.
- Requires in-patient hospitalization or prolongation of existing hospitalization. Hospitalizations that are not due to, or associated with, an AE should not be reported as an SAE, e.g., pre-planned hospitalizations for diagnostic tests.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is another important medical event*.

(*Other important medical events are those that may not result in death, be life-threatening, or require hospitalization, but may be considered an SAE when, according to appropriate medical judgment, they may jeopardize the patient and may require medical intervention to prevent one of the outcomes listed above).

10.2.8 Other Significant Adverse Events

Clinical laboratory abnormalities that qualify as AEs (other than those meeting the definition for serious) and any events that lead to an intervention (including premature discontinuation of Visipaque™ or saline, dose reduction or significant additional concomitant therapy), other than those reported as SAEs, will be reported and evaluated as other significant AEs.

10.2.9 Adverse Event and Serious Adverse Event Reporting

All AEs should be recorded from time of signing informed consent to the completion of Follow Up 3; acceptable diagnoses should be used, if possible. If an AE has already been reported, it is not necessary to report each individual sign and symptom of that AE as a separate AE. For example, if myocardial infarction is reported as an AE, there is no need to report elevated creatine kinase and abnormal ECG, or other related signs, symptoms, or laboratory values as separate AEs. However, if both occurred in isolation and myocardial infarction was not diagnosed, then each event would be reported as an AE.

The intensity of all AEs will be graded as mild, moderate, or severe using the following definitions:

Mild:	Tolerable.
Moderate:	Interferes with normal activity.
Severe:	Incapacitating (causes inability to perform usual activity or work)

The Investigator will be instructed to closely monitor each patient who experiences an AE (whether ascribed to Visipaque™ or saline or not) until the outcome of the AE has been determined.

In addition to the Investigator's own description of the AEs, each AE will be encoded by the Sponsor/CRO according to a well-recognized dictionary of medical codes.

All serious and non-serious AEs must be followed for a final outcome until the end of the follow-up period. An outcome of "unknown" is not considered to be an acceptable final outcome. An outcome of "not yet resolved" is an acceptable final outcome for non-serious AEs at the end of a patient's participation in a study, and for SAEs at database lock.

SAEs will be recorded in the eCRF if they occur as follows:

- After a patient first receives Visipaque™ or saline and throughout the patient's follow-up period,* whether or not considered related to Visipaque™ or saline, and
- After the patient's follow-up period, and for which a causal relationship to Visipaque™ or saline cannot be ruled out.

(*Follow-up period is defined as 6 months for SAEs and critical events reported for the purposes of adjudication or, for patients prematurely withdrawn from a study, the duration of a patient's participation.)

Investigators must report all SAEs to the Sponsor/CRO within 24 hours.

Details regarding how to notify the Sponsor/CRO of SAEs and contact details for any protocol or safety-related questions will be provided in a separate document.

The Sponsor/CRO (on behalf of the Sponsor) will report all SAEs to local health authorities, Independent Ethics Committees (IECs)/Independent Review Boards (IRBs) and Investigators as required by local regulations and Sponsor/CRO SOPs.

Patients enrolled at sites in the European Union will be provided with a Clinical Trial Participant card at the time of Visipaque™ or saline administration. This card will list contact details for the Investigator and for GE Healthcare medical emergency cover services (Clinical Trial Emergency Contact Service [CTECS]). The CTECS provides 24-hour, 7 day a week emergency cover service for healthcare professionals to seek advice on trial-related medical questions or problems should a medical emergency arise and the Investigator is not available.

10.2.10 Urgent Safety Measures

In accordance with the principles of Good Clinical Practice (GCP), the Investigator(s) has/have primary responsibility for assuring patient safety throughout the performance of study procedures. An urgent safety measure is defined as any measure which an Investigator may need to implement which is a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to trial patients without prior IEC/IRB approval/favorable opinion.

The Investigator may take appropriate urgent safety measures in order to protect the patients of a clinical trial against any immediate hazards to their health or safety. However, the Investigator must inform the Sponsor/CRO within 24 hours of having taken such measures.

The Sponsor in turn shall immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the licensing authority and the relevant IEC/IRB of the measures taken and the circumstances giving rise to those measures.

All urgent safety measures must be reported to the Sponsor/CRO by using the SAE contact numbers listed in Section 10.2.9 within 24 hours of having to take such a measure(s). Such reports can be initiated by telephone but must be officially documented by the Investigator (by email or fax) and must include details of what measures were taken and the circumstances giving rise to those measures.

10.2.11 Pregnancy Reporting

This process is aimed at ensuring the appropriate monitoring of the potential risk related to IMP exposure of pregnant women and/or fetuses as well as the risks associated with exposure of a father, regarding congenital abnormalities or birth defects in their offspring. It also ensures compliance with applicable international and local regulations.

The requirements are applicable to all patients following exposure to IMP.

Female trial patients: The trial patient must be advised by the Investigator to inform him/her immediately if she suspects she may be pregnant and believes that conception occurred within 30 days after administration of IMP.

Male trial patients: The trial patient must be advised by the Investigator to inform him/her immediately if they suspect their partner became pregnant within 30 days after the patient received an administration of IMP.

When a trial patient reports a pregnancy (post-IMP administration) to the Investigator, a pregnancy test should be arranged for the trial patient (or their partner) by the Investigator within 7 days of the pregnancy being reported.

The Investigator must inform the Sponsor/CRO within 24 hours of receiving positive pregnancy test results by using a copy of the relevant eCRF page (demography or AE) or via email. The Investigator should include an estimated date of conception when communicating with the Sponsor/CRO.

10.3 Other Variables

10.3.1 Demographic Data

Subject demographic data date of birth, race, gender, weight and height will be recorded at screening. Subject age at the time of randomization will be calculated from the date of birth and the date of baseline. BMI will be calculated from height and weight. If local regulations do not permit collection of specific demographic items e.g. date of birth, a dummy date will be used in accordance with local practice.

10.3.2 Medical and Surgical History

The subjects' relevant medical and surgical history will be recorded at Screening and Baseline.

10.3.3 Prior and Concomitant Medication and Procedures

Prior and concomitant medications and procedures will be recorded between Screening and Follow-up 3.

10.4 Appropriateness of Measurements

All assessments and measurements are appropriate and generally regarded as standard medical practice.

11 DATA HANDLING AND QUALITY ASSURANCE

11.1 Completing and Signing Case Report Forms

For eCRFs, data will be entered by trained site personnel with reasons given for any missing data. Any errors should be corrected within the electronic system. The audit trail will record all changes made, the date and time of the correction, and the person correcting the error and the reason for the correction. The appropriate electronic signature will be provided.

Any data recorded directly in the eCRF, for which no other written or electronic record will be maintained in the patient's medical record, will be considered source data and should be signed by the Investigator(s) (e.g., results of physical examinations, vital signs testing, or the Visipaque™ or saline placebo administration procedure).

11.2 Clinical Data Management

The Contract Research Organization (CRO) will be responsible for the processing and quality control of the data. Data management will be carried out by the CRO. The handling of data, including data quality control, will comply with all applicable regulatory guidelines.

11.3 Archiving

All study documentation at the Investigator site and Sponsor site will be archived in accordance with International Conference on Harmonisation (ICH) E6-GCP and the Sponsor/CRO's quality standards and standard operating procedures (SOPs).

All study documentation at the Investigator site and Sponsor site will be archived for a minimum of 15 years following completion or discontinuation of the study, unless notified otherwise by the Sponsor or a longer period is required by local legislation. The Principal Investigator is responsible for informing the Sponsor should he/she no longer be responsible for the study documentation and must provide details of the new responsible person. The Principal Investigator must request written agreement from the Sponsor before destruction of archived study documentation.

12 STATISTICAL METHODS AND PLANNED ANALYSIS

The data will be analyzed by the Sponsor and/or designated CRO. Any data analysis carried out independently by the Investigator should be submitted to the Sponsor before publication or presentation.

Data from participating centers in this protocol will be combined so that an adequate number of patients will be available for analysis. The data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, and safety observations and measurements.

12.1 General Statistical Considerations

Tabulations of summary statistics, graphical presentations, and statistical analyses will be performed with SAS® software, Version 9.2 or higher. Descriptive statistics for continuous data in summary tables will include the number of patients in the analysis (n), mean, standard deviation, median, and range (minimum, maximum). Descriptive statistics for categorical data in summary tables will include counts and percentages. The last observation prior to administration of Visipaque™ or saline placebo will be used as the baseline value for calculating changes from baseline after administration of Visipaque™ or saline placebo. All data obtained on the eCRF and entered into the database will be provided in separate data listings showing individual patient values. All summary tables and data listings will be separated by treatment groups. Statistical tests will use a 0.05 significance level for 2-sided tests and 0.025 for 1-sided tests. The planning and reporting of statistical analysis will be carried out as described in the Sponsor/CRO's SOPs governing clinical studies.

12.2 Definitions

CKD staging [National Kidney Foundation 2002] [Kirsztajn 2009]:

Stage I: kidney damage with normal or high GFR (≥ 90 mL/min/1.73 m²)

Stage II: kidney damage with mildly decreased GFR (60-89 mL/min/1.73 m²)

Stage IIIA: moderately reduced kidney function (GFR 45-59 mL/min/1.73 m²)

Stage IIIB: moderately reduced kidney function (GFR 30-44 mL/min/1.73 m²)

Stage IV: severely reduced kidney function (GFR 15-29 mL/min/1.73 m²)

Stage V: very severe or end-stage kidney failure (GFR < 15 mL/min/1.73 m²)

AKIN Serum Creatinine Criteria for AKI [AKIN 2015] [Mehta et al. 2007]:

Stage 1: a SCr increase of ≥ 0.3 mg/dL (≥ 26.4 μ mol/L) or increase to $\geq 150\%$ 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 $\mu\text{mol/L}$) with an acute increase of ≥ 0.5 mg/dL (≥ 44 $\mu\text{mol/L}$) within 48 hours

Standard definition of CIN [Mehran and Nikolsky 2006]:

Increase in SCr of 0.5 mg/dL or more in the 24 to 72 hours after the CT scan.

Waikar's definitions of AKI [Waikar and Bonventre 2009]:

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.

12.3 Populations for Analysis

12.3.1 Determination of Safety Population

The safety population will include all patients who are randomized to receive Visipaque™ or saline placebo and have post-randomization observations. This population will be based on the study treatment the patient is randomized to. Mortality and morbidity, image quality, and other safety outcome measures will be evaluated in the safety population.

12.3.2 Determination of Full Analysis Set

The full analysis set (FAS) will include all patients who receive Visipaque™ or saline placebo and have both baseline and post-scan SCr measurements. This population will also be based upon the treatment that the patient is randomized to. The FAS population will be the analysis population for primary, secondary and exploratory analyses.

12.3.3 Determination of Per-Protocol Set

The per-protocol (PP) set will include all patients who receive Visipaque™ or saline placebo, have both baseline and post-scan SCr measurements, and do not have any major protocol deviations with the potential of impacting data analyses and/or interpretability. This population will be based upon the treatment that the patient is randomized to. Patients in the saline placebo group who receive contrast medium prior to the 48 hour assessments (Follow-up 1) will be excluded from the analysis. Patients in the Visipaque™ group who receive additional doses of contrast medium prior to the 48 hour assessments (Follow-up 1) will also be excluded from the analysis. Primary, secondary and exploratory analyses will be repeated using the PP set.

12.4 Patient Demographics/Other Baseline Characteristics

A table will be provided with the following information:

- Number of patients enrolled.
- Number of patients included in the FAS.
- Number of patients included in the PP Set.
- Number of patients included in the Safety Population.
- Number of patients withdrawn from the study and the reason for withdrawal.

Demographic information (age, height, weight, and body mass index) will be summarized with descriptive statistics. Gender and race will be summarized by counts and percentages.

Medical histories will be summarized by counts and percentages. Concurrent medications will be recorded and coded by using a standard classification system and grouped by primary and secondary classes, if applicable.

12.5 Study Treatments

For each administration of Visipaque or saline placebo, the volume administered will be summarized. Additionally, hydration pre-scan and within 24 hours post-scan will be summarized in terms of oral, i.v., and total volume of fluids.

12.6 Primary Analysis

12.6.1 Variable

The primary variable is the incidence (proportion) of AKI stage ≥ 1 (by AKIN criteria) at 48 hours after intervention in patients with stage III or stage IV CKD.

12.6.2 Statistical Hypothesis, Model, and Method of Analysis

With P1 defined as the incidence of AKI stage ≥ 1 48 hours after i.v. administration of the iodinated iso-osmolar contrast material iodixanol (Visipaque™ Injection 320 mg-I/mL) and P2 defined as the incidence rate of AKI stage ≥ 1 48 hours after administration of saline placebo, the primary hypothesis to be tested for the primary analysis in the FAS is:

$$H_0: P1 - P2 \geq 0.05$$

$$H_1: P1 - P2 < 0.05$$

A 2-sided 95% confidence interval (CI) for noninferiority testing will be computed for the difference in sample incidence rates for the 2 treatment groups (CECT vs NECT, for the stage III and IV CKD patients combined) by the Miettinen and Nurminen method. If the upper bound of the 95% CI is less than 5%, then the noninferiority of Visipaque™ to the control (saline) will be concluded.

12.6.3 Handling of Missing Values/Censoring/Discontinuations

Missing values will not be imputed, and only observed values will be used in data analyses and reports, unless otherwise specified in the Statistical Analysis Plan (SAP).

12.6.4 Supportive Analyses

The incidence rates for the 2 treatment groups stratified by CKD stage and the associated 95% CIs will also be reported. The primary analysis will be repeated in the PP set by CKD stage and for stage III/IV combined.

In addition, a sensitivity analysis will be performed in the FAS adjusting for the covariates of total fluid intake pre-scan and total fluid intake within 24 hours post-scan. This analysis will be done by CKD stage and for stage III/IV combined.

12.7 Secondary Analyses

12.7.1 Secondary Variables and Analyses

The secondary hypothesis to be tested for the secondary endpoints that are proportions is the following:

$$H_0: P1 - P2 \geq 0.05$$

$$H_1: P1 - P2 < 0.05$$

The secondary hypotheses will be tested in patients in the FAS with CKD stage III and IV combined. The incidences for the 2 treatment groups (CECT vs NECT) will be compared by using the same statistical method as for the primary analysis.

AKI Secondary Endpoint Analyses:

The secondary endpoints of the study are:

Incidence of AKI stage ≥ 2 (by AKIN SCr criteria [AKIN 2015][Mehta et al. 2007]) following an i.v. injection of iodinated iso-osmolar contrast material iodixanol (Visipaque™ Injection 320 mg I/mL) or saline in patients with CKD stage III or IV. This analysis will be performed for the FAS assessed at 48 hours post-baseline (Follow-up 1).

Incidence of AKI (by standard definition of CIN [Mehran and Nikolsky 2006]) following an i.v. injection of iodinated iso-osmolar contrast material iodixanol (Visipaque™ Injection 320 mg I/mL) or saline in patients with CKD stage III or IV. This analysis will be performed for the FAS assessed at 48 hours post-baseline (Follow-up 1).

Incidence of AKI stage ≥ 2 (by Waikar criteria [Waikar and Bonventre 2009]) following i.v. administration of iodinated iso-osmolar contrast material iodixanol (Visipaque™ Injection 320 mg I/mL) or saline in patients with CKD stage III or IV. This analysis will be performed for the FAS assessed at 48 hours post-baseline (Follow-up 1).

In order to control the false positive rate at a one-sided 0.025 level across the testing of the secondary endpoints, the above endpoints will be tested hierarchically in the order given above. Each endpoint will be tested at a one-sided 0.025 level of significance; when a statistical test for a given endpoint fails to reach statistical significance in the appropriate direction, testing on all remaining secondary endpoints in the hierarchy will cease and the study will be considered successful on all secondary endpoints up to that point.

Secondary endpoint analyses will be repeated in the FAS for CKD stage III and IV separately and in the PP set by CKD stage and for stage III/IV combined.

Other Secondary Endpoint Analyses:

Other secondary endpoint analyses will be conducted using the safety population for stage III/IV combined. In addition, these summaries and analyses will be repeated for the stage III CKD subgroup and the stage IV CKD subgroup separately.

Mortality and morbidity events:

- All-cause death assessed at 6 months (Follow-up 3).
- Critical events (including EVAR-related post-baseline events as adjudicated by the CEAC) assessed at 6 months (Follow-up 3).
- Incidence rate of hospitalization due to renal failure assessed at 6 months (Follow-up 3).
- Incidence of requirement for renal replacement therapy (i.e., renal transplant, dialysis, or hemofiltration/ultrafiltration) assessed at 6 months (Follow-up 3).
- Incidence of the composite of death and hospitalization events due to renal failure assessed at 6 months (Follow-up 3).
- Hospital length of stay (LOS) in days assessed at 6 months (Follow-up 3).
- Incidence rate of patients with $\geq 30\%$ reduction in eGFR at 48 hours compared to baseline.
- Other criteria defined by the CEAC.

Image quality/diagnostic confidence analyses:

- No statistical comparisons between the CECT images and NECT images plus duplex ultrasonography images will be made.

12.7.2 Exploratory Analyses

[REDACTED]

12.7.3 Other Safety Variables and Analyses

Other safety variables will be analyzed for the Safety Population.

In addition to the Investigator's evaluation of normal or abnormal, the Sponsor will internally evaluate clinical laboratory, vital-sign, and ECG results for an outlying result or extreme value as follows:

- An outlying result for any numeric laboratory result, vital-sign result, or ECG interval measurement will be any post-administration change from baseline that meets either of the following criteria:
 $<25\text{th Percentile} - 1.5 * (\text{interquartile range})$ OR
 $>75\text{th Percentile} + 1.5 * (\text{interquartile range})$.
- An extreme value for any numeric laboratory result, vital-sign result, or ECG interval measurement will be any post-administration change from baseline that meets either of the following criteria:
 $<25\text{th Percentile} - 3 * (\text{interquartile range})$ OR
 $>75\text{th Percentile} + 3 * (\text{interquartile range})$.

Post-administration changes from baseline will be summarized by mean, SD, minimum, and maximum at each time point for each treatment group (CECT vs NECT). Plots and shift tables of all post-administration changes from baseline vs time will be generated and examined for trends and relatively large individual changes from baseline.

12.7.3.1 Clinical Laboratory Evaluation

Descriptive statistics will be displayed for the observed values and changes from baseline. In addition, for each clinical laboratory variable and each time point, the following safety endpoints will be summarized by counts and percentages by treatment group (CECT vs NECT):

- The occurrence of 1 or more changes from baseline, at each post-administration time point, greater than 40% and 80% of the span of the normal limits (not applicable to qualitative parameters).
- The occurrence of post-administration values outside the normal limits (not applicable to qualitative parameters). Shift tables based on the normal range will be prepared.

12.7.3.2 Vital Signs

Descriptive statistics will be displayed for the observed values and changes from baseline. For each vital-sign variable and each time point, the following safety endpoints will be summarized by counts and percentages by treatment group (CECT vs NECT):

- The occurrence of 1 or more changes from baseline, at each post-administration time point, greater than a prespecified magnitude (20 mm Hg for systolic blood pressure, 10 mm Hg for diastolic blood pressure, 10 beats/minute for heart rate and 10 breaths/minute for respiration rate).

- The occurrence of post-administration values outside the normal limits (Section 15.3). Shift tables based on the normal range will be prepared.

12.7.3.3 Physical Examination

The number and percentage of patients with changes in physical examination status from normal at baseline to abnormal at each post-administration time point (and vice versa) will be presented by treatment group (CECT vs NECT). Shift tables based on the normal range will be prepared.

12.7.3.4 Adverse Events

AEs and SAEs will be coded using MedDRA and all reported events will be listed for the safety population. Treatment-emergent AEs are defined as AEs that occur from the time of treatment administration through Follow-Up 3. The number and percentage of patients with 1 or more AEs will be summarized by system organ class and preferred term overall and by treatment group (CECT vs NECT). Summaries will also be presented by AE intensity and judged relationship to Visipaque™ or saline placebo. Treatment-emergent SAEs are defined as SAEs that occur from the time of treatment administration through Follow-Up 3. Treatment-emergent SAEs will be presented by treatment group for the safety population.

12.8 Sample Size Calculation

The primary endpoint is the incidence rate (proportion) of AKI stage ≥ 1 (by AKIN SCr criteria) at 48 hours after intervention in patients with stage III or stage IV CKD. With P1 defined as the incidence rate of AKI stage ≥ 1 following i.v. administration of Visipaque™ and P2 defined as the incidence rate of AKI stage ≥ 1 following administration of saline placebo, the sample size estimate is based on the following assumptions and statistical method:

- (1) Both P1 and P2 are 10%
- (2) A noninferiority margin of 5%
- (3) Power of 80% using the 95% CI of P1 – P2
- (4) The score test [Miettinen and Nurminen 1985] with a 1-sided 0.025 significance level is employed

A sample size of 1164 randomized patients (582 per treatment group) in the FAS will provide 80% power to demonstrate noninferiority of the proportion of AKI stage ≥ 1 (by AKIN criteria) in patients receiving Visipaque™ Injection 320 mgI/mL as compared with patients receiving the saline placebo.

To compensate for a screen failure rate of approximately 15%, approximately 1370 patients will be screened.

It is expected that the number of patients who are excluded from the PP set will be small, resulting in minimal loss of statistical power. However, the number of patients excluded from

the PP set will be monitored and the sample size may be increased as needed to maintain adequate statistical power to repeat the primary analysis in the PP set.

A blinded sample size re-estimation will be performed after 50% of patients are enrolled and adjudicated by the CEAC. The calculation will be made by an independent statistician and will be based on the blinded, overall rate of AKI as determined by the CEAC. The purpose of this re-evaluation is to confirm assumptions made about the rate of AKI in the planned sample size calculation. No re-estimation of the difference between treatments or the NI margin will be done. In a blinded sample size re-estimation of the overall event rate in a non-inferiority trial with a binary endpoint, there is no notable effect on the Type I error rate [Friede et al. 2007] and, therefore, no alpha adjustments will be made in the final analysis. Based on the results of the re-estimation, the Steering Committee may recommend to stop enrollment if the new sample size is already exceeded, continue with the planned sample size, or increase the sample size to maintain adequate statistical power. Details of the sample size re-estimation methodology will be pre-defined in the SAP.

12.9 Procedures for Missing, Unused, and Spurious Data

Missing values will not be substituted by estimated values but treated as missing in the statistical evaluation unless otherwise specified in the SAP. All data from all patients dosed in the study will be included in all listings, plots, summary tables, and statistical analyses when appropriate.

12.10 Rules for Excluding Patients from Analysis

All randomized patients with any post-randomization observations will be included in the analyses unless otherwise specified in the SAP. The Sponsor will make any decisions regarding whether any patients or any individual values belonging to a patient will be excluded from the evaluations when the protocol violation is considered to have a negative impact on the scientific aspects and interpretation of the study results. Such judgments should be made in a blinded fashion before database lock and before any analyses have been performed. If the patient has been randomized to receive Visipaque™ or saline placebo and has post-randomization observations, all available safety data will be used. The reason(s) for any exclusion will be described in the report.

12.11 Procedures for Reporting Deviations from Original Statistical Plan

Any deviations from the statistical analysis outlined in this protocol will be described, and reasons for the deviations listed, in the final Clinical Study Report.

13 SPECIAL REQUIREMENTS AND PROCEDURES

13.1 Regulatory, Institutional and Ethical Review

Before starting this study, the Protocol (authorized by the Sponsor) will be submitted to the regulatory bodies/local health authorities (in accordance with local regulations) and to the IEC/IRB for evaluation. The Protocol will also be signed by the Principal Investigator before submission to the IEC/IRB. The study will not start before the IEC/IRB gives written approval or a favorable opinion in accordance with ICH E6-GCP and all applicable regulatory bodies/local health authorities give approval or a favorable opinion as required.

No changes from the final approved (authorized) protocol will be initiated without the IEC's/IRB's prior written approval or favorable opinion of a written amendment, except when necessary to eliminate immediate hazards to the patients or when the change involves only logistics or administration. The Sponsor will authorize and the Principal Investigator(s) will sign the protocol amendment prior to submission to the IEC/IRB. Protocol amendments should be submitted to the IEC/IRB without delay.

13.2 Investigator's Responsibilities

13.2.1 Overall Responsibilities

The Investigator(s) is/are responsible for conducting the study in full accordance with the Protocol and the Declaration of Helsinki, the *Good Clinical Practice: Consolidated Guideline*, approved by the ICH, and any applicable national and local laws and regulations. Information regarding any investigational centers participating in this study that cannot comply with these standards will be documented.

13.2.2 Patient Informed Consent

Written and oral information about the study in a language understandable by the patient will be given to all patients. Each patient's willingness to participate in the study will be documented in a signed and dated informed consent form, approved by the relevant IRB/EC and the Sponsor, before any procedures or assessments are done and after the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force are explained. It will also be explained to the patients that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. The informed consent process will be documented in the patient's medical record; and the Investigator will sign, date, and time the informed consent form after the patient has signed, dated, and recorded the time. The Investigator(s) will keep the original consent forms, and copies will be given to the patients.

13.2.3 Direct Access to Source Data/Documents

The monitor(s), auditor(s), authorized personnel of the Sponsor/CRO, health authority inspector(s) or their agents, and authorized members of IECs/IRBs will be given direct access to source data and documentation (e.g., medical charts/records, laboratory results, printouts, videotapes) for source data verification, provided that patient confidentiality is maintained in accordance with local requirements.

13.2.4 Confidentiality Regarding Study Patients

The Investigator(s) must assure that the privacy of the patients, including their personal identity and all other personal medical information, will be maintained at all times. In eCRFs and other documents or image material (including materials from all examinations [e.g., CT and ultrasound examinations]) submitted to the Sponsor/CRO, patients will not be identified by their names, but by an identification code (e.g., study patient number).

Personal medical information may be scrutinized for the purpose of verifying data recorded in the eCRF. This may be done by the monitor(s), properly authorized persons on behalf of the Sponsor, the quality assurance unit, or regulatory authorities. Personal medical information will always be treated as confidential.

13.3 Protocol Deviations

Any deviation from the protocol when no approved amendment exists must be documented as a protocol deviation and reported according to local requirements. If appropriate, corrective and preventative action must be implemented to avoid repetition. Protocol deviations and any potential impact on the study results will be discussed during the reporting of the study.

Waivers or protocol exceptions will not be granted prospectively by the Sponsor under any circumstances.

13.4 Study Monitoring

The Sponsor has ethical, legal and scientific obligations to carefully follow this study protocol in a detailed and orderly manner, in accordance with established research principles and applicable regulations. The Investigator, as part of his responsibilities, is expected to cooperate with the Sponsor in ensuring that the protocol and GCP requirements are adhered to.

Study monitoring will be performed in accordance with ICH E6-GCP, the Sponsor/CRO SOPs, the protocol, and applicable local regulations.

In order to fulfil these obligations, the Sponsor will authorize a CRO to perform monitoring on its behalf. The Investigator will be expected to permit CRO personnel to monitor the study as frequently as is deemed necessary and to provide access to medical records to ensure that the

protocol is being adhered to, data are accurate and verifiable and that the safety and wellbeing of patients is being maintained.

13.5 Audit and Inspection

According to ICH E6-GCP, the Sponsor or regulatory authorities may audit or inspect the Investigational Site at any time during the study. The Sponsor's Quality Assurance Unit, independent of the Clinical Research and Development Department, is responsible for auditing the study and may appoint a CRO to perform some or all of the audit activities.

The Investigator(s) must accept that regulatory authorities may conduct an inspection to verify compliance of the study with GCP.

13.6 Insurance

This study is covered under the Sponsor's Liability Insurance Policy (under General Electric Insurance Company and/or a company designated by the study Sponsor). A Certificate of Insurance and/or an information leaflet containing essential information about the insurance coverage can be provided upon request.

13.7 Publication Policy

Presentations, abstracts, posters, publications and any other scientific communications regarding the study protocol, conduct, and results shall be managed by the study Steering Committee through a Publication Committee. The Publication Committee shall have the right to publish the results of their work conducted under this protocol, subject to providing the Sponsor with the opportunity to review the contents of any proposed abstract or publication concerning the work, including any results of the study, in advance of publication and if necessary to delay publication for a limited time not to exceed 60 days in order to protect the confidentiality or proprietary nature of any information contained therein. The Sponsor will make every reasonable effort to consider and release each proposed publication within 30 days, or proposed abstract within 15 days, of submission. Investigators shall comply with this policy.

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15 APPENDICES

15.1 Information on Investigational and Registered Products

The reference document for this phase 4 study in an approved indication and within boundaries of approved product information for Visipaque™ is the current IB. This reference document provides up-to-date information on the efficacy and safety of Visipaque™ Injection 320 mg/mL. The safety profile of Visipaque™ is based on clinical and extensive postmarketing surveillance experience. Section 6.2.3.8 (Undesirable effects) of the IB will be used for assessing expectedness of Serious Adverse Drug Reactions (SADRs), in order to determine regulatory reportability. An unexpected ADR is a reaction whose nature, seriousness, severity, or outcome is not consistent with the applicable product information.

15.2 Equipment Parameters

Equipment parameters will be described in the Imaging Manuals.

15.3 Normal Limits for Vital Signs

Table 3 Criteria for Normal Limits for Vital Signs

Vital Signs Parameter	Normal Limits	
	Low	High
Systolic BP (mm Hg)	85	139
Diastolic BP (mm Hg)	60	89
Heart rate (beats/minute)	60	100
Respiration rate (breaths/minute)	12	22
Body weight (kg) ^a	41	113
Body mass index (kg/m ²) ^b	18.5	24.9

^a Changes in body weight are evaluated by the Investigator (without taking height into account) since BMI is not collected on the eCRF.

^b BMI is calculated and analyzed retrospectively by the Sponsor, at which time height is taken into account.

16 CLINICAL PROTOCOL AMENDMENT SUMMARIES

16.1 Amendment A01

16.1.1 Reasons for Amendment

- Information on the recent ESC 2014 guidelines is added.
- Clarification that the subset of patients who may also receive MB-102 and be monitored by ORFM will 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 are more fully defined.
- Clarification of hydration requirements and the use of 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 is updated.
- Minor typographical errors are corrected.

Where appropriate, the changes documented below are also made in the synopsis. Where appropriate the changes are indicated in *italics*.

16.1.2 Description of Changes

Section 4, Background Information and Study Rationale, Tenth Paragraph

Previously Read:

There is no universally accepted imaging protocol for post-EVAR surveillance (e.g., for detection of endoleaks, detection of mechanical changes in the stent-graft, and evidence of expansion or shrinkage of the residual sac). The American College of Radiology notes that computed tomography angiography (CTA) is considered the gold standard for the diagnosis of endoleaks [ACR 2012]. In 2010, the Society of Interventional Radiology published clinical practice guidelines for EVAR [Walker et al 2010]. These guidelines, which were endorsed by the Cardiovascular and Interventional Radiological Society of Europe and the Canadian Interventional Radiology Association, indicated that even though CTA is the most commonly used examination for post-EVAR surveillance, unenhanced CT, magnetic resonance

angiography, ultrasonography, and even simple radiography, remain commonly used and appropriate. In practice, vascular surgeons do not always follow these guidelines; and if the results of the first post-EVAR CTA are negative, unenhanced CT or ultrasonographic exams are often ordered instead of CTA for continued surveillance. Thus, after the first post-EVAR examination, there is clinical equipoise between imaging methods that do and do not require administration of contrast medium. As a result, it is ethically acceptable to use randomization to assign some patients to receive contrast medium and some patients to be evaluated without the use of contrast medium.

Now Reads:

There is no universally accepted imaging protocol for post-EVAR surveillance (e.g., for detection of endoleaks, detection of mechanical changes in the stent-graft, and evidence of expansion or shrinkage of the residual sac). The American College of Radiology notes that computed tomography angiography (CTA) is considered the gold standard for the diagnosis of endoleaks [ACR 2012]. In 2010, the Society of Interventional Radiology published clinical practice guidelines for EVAR [Walker et al 2010]. These guidelines, which were endorsed by the Cardiovascular and Interventional Radiological Society of Europe and the Canadian Interventional Radiology Association, indicated that even though CTA is the most commonly used examination for post-EVAR surveillance, unenhanced CT, magnetic resonance angiography, ultrasonography, and even simple radiography, remain commonly used and appropriate. *The recent ESC 2014 Guideline on the diagnosis and treatment of aortic diseases is also largely in line with guidelines published earlier in terms of imaging follow-up recommendations, and the use of color-Doppler US can be considered as an alternative in case neither endoleak nor abdominal aortic aneurysm sac enlargement was documented during the first year after EVAR [ESC Guidelines 2014].* In practice, vascular surgeons do not always follow these guidelines; and if the results of the first post-EVAR CTA are negative, unenhanced CT or US exams are often ordered instead of CTA for continued surveillance. Thus, after the first post-EVAR examination, there is clinical equipoise between imaging methods that do and do not require administration of contrast medium. As a result, it is ethically acceptable to use randomization to assign some patients to receive contrast medium and some patients to be evaluated without the use of contrast medium.

Section 6.1, Overall Study Design and Plan, Second Paragraph

Previously Read:

The patients will be randomly assigned to undergo either CECT or NECT for this routine surveillance CT examination (full details are provided in the CT Imaging Manual). Patients in the CECT arm will receive a 100-mL i.v. injection of iodixanol (Visipaque Injection 320 mg I/mL), followed by a 10 mL saline flush, for enhancement of the CT examination. Patients in the NECT arm will receive a volume-matched i.v. injection of a saline placebo, followed by a 10 mL saline flush, before their CT examination. All patients (CECT and NECT arms) will be required to drink 500 mL of water following collection of blood samples for

central analysis of SCr and prior to scanning and be encouraged to drink at least 2500 mL of water in the 24 hours immediately following CT scanning.

Now Reads:

The patients will be randomly assigned to undergo either CECT or NECT for this routine surveillance CT examination (full details are provided in the CT Imaging Manual). Patients in the CECT arm will receive a 100-mL i.v. injection of iodixanol (Visipaque Injection 320 mg I/mL), followed by a 10 mL saline flush, for enhancement of the CT examination. Patients in the NECT arm will receive a volume-matched i.v. injection of a saline placebo, followed by a 10 mL saline flush, before their CT examination. All patients (CECT and NECT arms) will be required to drink 500 mL of *fluids* following collection of blood samples for central analysis of SCr and prior to scanning. All patients (*CECT and NECT arm*) will be *required* to drink at least 2500 mL of *fluids* in the 24 hours immediately following CT scanning. *To ensure a consistent approach, oral hydration is preferred, however, in case of concern about the patient's compliance and/or capability to follow the oral hydration instructions, i.v. administration of isotonic crystalloid solution (saline or bicarbonate) may be considered. In case of i.v. administration of crystalloids, the combination of oral and i.v. fluids must equal a minimum of 500 mL pre-contrast material administration and 2500 mL within 24 hours post-contrast material administration. Subjects will be asked to record their fluid intake. The volume of fluids, before and within 24 hours after administration, must be carefully documented in source records and in the CRF. Decision on use of i.v. hydration will be made and documented before randomization and implemented regardless of whether the subject is randomized to the NECT or CECT arm.*

Section 6.1, Overall Study Design and Plan, Final Paragraph

Previously Read:

A subset of patients (no more than 100), at selected sites, may also receive the inert fluorescent agent MB-102 (manufactured by MediBeacon, Saint Louis, MO, USA) and will be monitored by ORFM (Sections 8.1.3 and 9.2.3).

Now Reads:

A subset of patients (no more than 100), at selected sites *in the USA*, may also receive the inert fluorescent agent MB-102 (manufactured by MediBeacon, Saint Louis, MO, USA) and will be monitored by ORFM (Sections 8.1.3 and 9.2.3).

Section 6.3, Risks and Benefits to Patients, Fourth Paragraph**Previously Read:**

There is no universally accepted imaging protocol for post-EVAR surveillance (e.g., for detection of endoleaks, detection of mechanical changes in the stent-graft, and evidence of expansion or shrinkage of the residual sac). The American College of Radiology notes that computed tomography angiography (CTA) is considered the gold standard for the diagnosis of endoleaks [ACR 2012]. In 2010, the Society of Interventional Radiology published clinical practice guidelines for EVAR [Walker et al 2010]. These guidelines, which were endorsed by the Cardiovascular and Interventional Radiological Society of Europe and the Canadian Interventional Radiology Association, indicated that even though CTA is the most commonly used examination for post-EVAR surveillance, unenhanced CT, magnetic resonance angiography, ultrasonography, and even simple radiography, remain commonly used and appropriate. In practice, vascular surgeons do not always follow these guidelines; and if the results of the first post-EVAR CTA are negative, unenhanced CT or ultrasonographic exams are often ordered instead of CTA for continued surveillance. Thus, after the first post-EVAR examination, there is clinical equipoise between imaging methods that do and do not require administration of contrast medium. As a result, it is ethically acceptable to use randomization to assign some patients to receive contrast medium and some patients to be evaluated without the use of contrast medium.

Now Reads:

There is no universally accepted imaging protocol for post-EVAR surveillance (e.g., for detection of endoleaks, detection of mechanical changes in the stent-graft, and evidence of expansion or shrinkage of the residual sac). The American College of Radiology notes that computed tomography angiography (CTA) is considered the gold standard for the diagnosis of endoleaks [ACR 2012]. In 2010, the Society of Interventional Radiology published clinical practice guidelines for EVAR [Walker et al 2010]. These guidelines, which were endorsed by the Cardiovascular and Interventional Radiological Society of Europe and the Canadian Interventional Radiology Association, indicated that even though CTA is the most commonly used examination for post-EVAR surveillance, unenhanced CT, magnetic resonance angiography, ultrasonography, and even simple radiography, remain commonly used and appropriate. *The recent ESC 2014 Guideline on the diagnosis and treatment of aortic diseases is also largely in line with guidelines published earlier in terms of imaging follow-up recommendations, and the use of color-Doppler US can be considered as an alternative in case neither endoleak nor abdominal aortic aneurysm sac enlargement was documented during the first year after EVAR [ESC Guidelines 2014].* In practice, vascular surgeons do not always follow these guidelines; and if the results of the first post-EVAR CTA are negative, unenhanced CT or ultrasonographic exams are often ordered instead of CTA for continued surveillance. Thus, after the first post-EVAR examination, there is clinical equipoise between imaging methods that do and do not require administration of contrast medium. As a result, it is ethically acceptable to use randomization to assign some patients to receive contrast medium and some patients to be evaluated without the use of contrast medium.

Section 7.3, Inclusion Criteria #4 and #5**Previously Read:**

- (4) Has previously completed his or her first post-EVAR surveillance imaging examination (usually performed around 1-month).
- (5) Has a documented diagnosis of stage III or IV (defined as $30 \leq$ estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² and $15 \leq$ eGFR <30 mL/min/1.73 m², respectively, according to the Modification of Diet in Renal Disease [MDRD] equation) CKD and stable renal function (last 2 SCr values within ± 0.5 mg/dL of each other, with the most recent value within 5 days prior to the scheduled CT examination and the preceding value within 12 months).

Now Reads:

- (4) Has previously completed his or her first post-EVAR surveillance *CECT* imaging examination (usually performed around 1-month).
- (5) Has a documented diagnosis of stage III or IV (defined as $30 \leq$ estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² and $15 \leq$ eGFR <30 mL/min/1.73 m², respectively, according to the Modification of Diet in Renal Disease [MDRD] equation) CKD and stable renal function (last 2 SCr values within ± 0.5 mg/dL of each other, with the most recent value within 7 days prior to the scheduled CT examination and the preceding value within *1 to 12 months before that*).

Section 7.3, Exclusion Criteria #15 and #16**Previously Read:**

- (15) Has used nonsteroidal anti-inflammatory drugs (NSAIDs) or any nephrotoxic medication within 48 hours of the Baseline Visit or will do so within 72 hours after the CT procedure (renal function must be evaluated before any nephrotoxic medication is resumed).
- (16) Has been hospitalized within 30 days prior to Screening Visit.

Now Reads:

- (15) Has used nonsteroidal anti-inflammatory drugs (NSAIDs) or any nephrotoxic medication within 48 hours of the Baseline Visit or will do so within 72 hours after the CT procedure (renal function must be evaluated before any nephrotoxic medication is resumed) – *with the exception of acetylsalicylic acid (Aspirin) at a dose of ≤ 100 mg daily (QD)*.

- (16) Has been hospitalized within 30 days prior to Screening Visit *for any reason other than practical purposes for management of tests or diagnostic assessments.*

Section 8.1.3, Optical Renal Function Monitoring, First Paragraph, First Sentence

Previously Read:

A subset of patients (no more than 100), at selected sites, may also receive an inert fluorescent pyrazine-based tracer agent (MB-102), which is used with an ORFM to enable accurate tracking of kidney function, by non-invasively measuring fluorescent light emission over time.

Now Reads:

A subset of patients (no more than 100), at selected sites *in the USA*, may also receive an inert fluorescent pyrazine-based tracer agent (MB-102), which is used with an ORFM to enable accurate tracking of kidney function, by non-invasively measuring fluorescent light emission over time.

Section 8.5, Prior and Concurrent Medications or Procedures (previously Prior and Concurrent Therapy)

Previously Read:

Any medications taken by the patient within 14 days before Visipaque™ or saline placebo administration and up to the end of Follow-Up 3 will be recorded in the eCRF along with the indication for use and dosage. Either the generic or the trade name may be recorded. The Sponsor/CRO will encode all therapy and medication according to a current well-recognized dictionary of medical codes.

Now Reads:

Any medications taken by the patient, *medical procedure, or diagnostic assessment* within within 14 days before Visipaque™ or saline placebo administration and up to the end of Follow-Up 3 will be recorded in the eCRF along with the indication for use and dosage. Either the generic or the trade name may be recorded. The Sponsor/CRO will encode all therapy and medication according to a current well-recognized dictionary of medical codes.

Metformin, NSAIDs, and drugs with nephrotoxic potential will be required to be discontinued temporarily per exclusion criteria #5 and #15, and the current use of i.v. vasopressor or inotropic medications is prohibited per exclusion criterion #14. The prophylactic use of acetylsalicylic acid (Aspirin) in a dose of ≤ 100 mg QD is permitted.

Section 9, Study Procedures, Table 1, Study Schedule of Event**Previously Read:****Table 1 Study Schedule of Events**

Parameter	Screening Visit (within -5 days) ^a	Baseline Visit			Follow-Up 1 (Baseline +48 hours ±6 hours)	Follow-Up 2 (Baseline +7 days ±2 days) ^c	Follow-Up 3 (Baseline + 6 months ±2 weeks) ^d
		Pre-Scan ^a	Scan	Post Scan ^b			
Informed consent	X						
Inclusion/exclusion criteria	X ^a	X ^a					
Demographic information	X ^a	X ^a					
Medical/surgical history	X ^a	X ^a					
Prior/concomitant medication	X ^a	X ^a			X	X	X
Physical examination	X ^a	X ^a				X ^c	
Electrocardiogram (12-lead)	X ^a						
Vital signs ^e	X ^a	X ^a		X	X	X ^c	
Pregnancy test (if indicated) ^f	X	X					
Randomization to CECT or NECT arm		X					
Blood and urine sampling for screening SCr, clinical chemistry, hematology (local laboratory) ^g	X						
Blood sampling for SCr, cystatin C, and N-GAL (central laboratory) ^g		X			X	X ^c	X ^d
Urine sampling for NephroCheck® biomarkers (local laboratory, if available) ^g		X		X	X		
Adverse events	X	X		X	X	X	X
Serious adverse events and critical events as per CEAC ^h	X	X		X	X	X	X ^d
Oral hydration (500 mL)		X					
ORFM (selected sites only)		X		X			
Saline administration (NECT arm only)			X				
Visipaque™ injection 320 mgI/mL administration (CECT arm only)			X				
CT scan ⁱ			X				
Reminder re: oral hydration (water 2500 mL) ^j				X			

Table 1 Study Schedule of Events

Parameter	Screening Visit (within -5 days) ^a	Baseline Visit			Follow-Up 1 (Baseline +48 hours ±6 hours)	Follow-Up 2 (Baseline +7 days ±2 days) ^c	Follow-Up 3 (Baseline + 6 months ±2 weeks) ^d
		Pre-Scan ^a	Scan	Post Scan ^b			
Non-contrast duplex ultrasonography (NECT arm only) ^k				X			

CEAC = Critical Events Adjudication Committee; CECT = contrast-enhanced computed tomography; NECT = nonenhanced computed tomography; ORFM = optical renal function monitor ; SCr = serum creatinine

^a Some procedures from the Screening Visit may be performed at the Baseline Visit for patient convenience; however, informed consent must be obtained from 5 days prior and up to a minimum of 24 hours prior to the Baseline Visit.

^b Within 4 hours after scanning.

^c If results obtained at Follow-Up 1 meet primary criteria (AKI stage ≥ 1 , per AKIN), Follow-Up 2 will be performed as a clinic visit. A telephone follow-up will be performed for all other patients. If the patient attends the clinic, the following will be performed: concomitant medication will be recorded, vital signs will be recorded, blood samples for clinical chemistry will be collected, physical examination, adverse events and critical events will be recorded. If the patient receives a telephone follow-up, the following will be recorded: concomitant medication, adverse events and critical events.

^d A blood sample for SCr will be collected either at the patient's home (if this service is locally available) or at the study center, and SAEs and critical events will be recorded either by telephone (for patients receiving a home visit) or at the study center.

^e Vital signs are to be measured in the sitting position. The patient should rest for at least 5 minutes before vital signs measurement.

^f If applicable, a negative urine pregnancy test must be obtained at the Screening and Baseline Visit for female patients

^g All blood samples taken prior to dosing and following the scan will be taken from venous blood. Local laboratories will be used for determination of eligibility for the trial and for stratification during randomization. A central laboratory will be utilized for analysis of SCr, cystatin C, and N-GAL collected at the Baseline Visit, Follow-Up 1 and Follow-Up 2 (for patients meeting primary AKIN criteria at Follow-Up 1). Urine samples collected for NephroCheck® biomarkers (TIMP-2 and IGFBP-7) for patients where local NephroCheck® testing is available will be taken just before the scan, 4 hours post scan, and at 48 hours post scan

^h Critical events, including EVAR-related post-baseline events, will be collected from administration to approximately 6 months after administration of Visipaque™ Injection for assessment by the CEAC.

ⁱ CT scan according to correct acquisition protocol

^j 2500 mL water recommended to be consumed within the 24 hours post-CT period

^k Non-contrast duplex ultrasonography will be performed ideally on the same day as NECT imaging and within 2 days of performing the NECT according to correct acquisition protocol

Now Reads:**Table 1 Study Schedule of Events**

Parameter	Screening Visit (within -7 days) ^a	Baseline Visit			Follow-Up 1 (Baseline +48 hours ±6 hours) ^d	Follow-Up 2 (Baseline +7 days ±2 days) ^c	Follow-Up 3 (Baseline + 6 months ±2 weeks) ^d
		Pre-Scan ^a	Scan	Post Scan ^b			
Informed consent <i>signed</i>	X						
Inclusion/exclusion criteria	X ^a	X ^a					
Demographic information	X						
Medical/surgical history	X ^a	X ^a					
Prior/concomitant medication <i>or procedures</i>	X ^a	X ^a			X	X	X
Physical examination	X ^a	X ^a				X ^c	
Electrocardiogram (12-lead)	X						
Vital signs ^e	X ^a	X ^a		X	X	X ^c	
Pregnancy test (if indicated) ^f	X	X					
Randomization to CECT or NECT arm		X					
Blood and urine sampling for screening SCr, clinical chemistry, hematology (local laboratory) ^g	X						
Blood sampling for SCr, cystatin C, and N-GAL (central laboratory) ^g		X			X	X ^c	X ^d
Urine sampling for NephroCheck® biomarkers (local laboratory, if available) ^g		X		X	X		
Adverse events	X	X		X	X	X	X
Serious adverse events and critical events as per CEAC ^h	X	X		X	X	X	X ^d
Hydration (500 mL) ⁱ		X					
ORFM (selected sites only)		X		X			
Saline administration (NECT arm only)			X				
Visipaque™ injection 320 mgI/mL administration (CECT arm only)			X				
CT scan ^j			X				
Non-contrast duplex ultrasonography (NECT arm only) ^k				X			
Reminder re: hydration (2500 mL) ⁱ				X			
Record hydration volume		X		X	X		

Table 1 Study Schedule of Events

Parameter	Screening Visit (within -7 days) ^a	Baseline Visit			Follow-Up 1 (Baseline +48 hours ±6 hours) ^d	Follow-Up 2 (Baseline +7 days ±2 days) ^e	Follow-Up 3 (Baseline + 6 months ±2 weeks) ^d
		Pre-Scan ^a	Scan	Post Scan ^b			

CEAC = Critical Events Adjudication Committee; CECT = contrast-enhanced computed tomography; NECT = nonenhanced computed tomography; ORFM = optical renal function monitor ; SCr = serum creatinine

^a Screening procedures may be conducted on the same day as baseline pre-scan assessments, dependent on the site's local laboratory turnaround time for Scr. In this instance assessments required for screening and baseline pre-scan need only be conducted once. If the screening and baseline assessments occur on separate days, the assessments need to be completed at each visit. A signed consent must be obtained from 7 days prior to the Baseline Visit and before any study screening or pre-scan assessments are conducted

^b Within 4 hours after scanning.

^c If results obtained at Follow-Up 1 meet primary criteria (AKI stage ≥ 1 , per AKIN), Follow-Up 2 will be performed as a clinic visit. A telephone follow-up will be performed for all other patients. If the patient attends the clinic, the following will be performed: concomitant medication will be recorded, vital signs will be recorded, blood samples for clinical chemistry will be collected, physical examination, adverse events and critical events will be recorded. If the patient receives a telephone follow-up, the following will be recorded: concomitant medication, adverse events and critical events.

^d A blood sample for SCr will be collected either at the patient's home (if this service is locally available) or at the study center, and SAEs and critical events will be recorded either by telephone (for patients receiving a home visit) or at the study center.

^e Vital signs are to be measured in the sitting position. The patient should rest for at least 5 minutes before vital signs measurement.

^f If applicable, a negative urine pregnancy test must be obtained at the Screening and Baseline Visit for female patients

^g All blood samples taken prior to dosing and following the scan will be taken from venous blood. Local laboratories will be used for determination of eligibility for the trial and for stratification during randomization. A central laboratory will be utilized for analysis of SCr, cystatin C, and N-GAL collected at the Baseline Visit, Follow-Up 1 and Follow-Up 2 (for patients meeting primary AKIN criteria at Follow-Up 1). *Sampling for Follow-Up 1 should occur as close to 48 hours as possible to support the primary endpoint assessment for AKI [ACR 2015], with use of the -6 hour window being preferable to use of the +6 hour window.* Urine samples collected for NephroCheck® biomarkers (TIMP-2 and IGFBP-7) for patients where local NephroCheck® testing is available will be taken just before the scan, 4 hours post scan, and at 48 hours post scan

^h Critical events, including EVAR-related post-baseline events, will be collected from administration to approximately 6 months after administration of Visipaque™ Injection/ saline placebo for assessment by the CEAC.

ⁱ 500 mL of fluids after SCr sampling and before the CT scan to be consumed. 2500 mL of fluids within the 24 hours post-CT period to be consumed. In case of concern about the patient's compliance and/or capability to follow the oral hydration instructions, i.v. administration of isotonic crystalloid solution (saline or bicarbonate) may be considered. Decision on use of i.v. hydration to be made and documented prior to randomization and performed regardless of whether the patient is randomized to the NECT or CECT arm

^j CT scan according to correct acquisition protocol

^k Non-contrast duplex ultrasonography will be performed ideally on the same day as NECT imaging and within 2 days of performing the NECT according to correct acquisition protocol

Section 9.1, Screening Visit**Previously Read:**

A Screening visit will take place up to 5 days before a scheduled CT examination for post-EVAR surveillance.

At the Screening visit, the following will be collected and/or performed:

- Written informed consent.
- Demographic information.
- General medical/surgical history.
- Prior and concomitant medications.
- All female patients of child-bearing potential will undergo a urine pregnancy test.
- Physical examination.
- Vital signs (blood pressure, heart rate, respiration rate) in the sitting position.
- 12-lead electrocardiogram (ECG).
- Blood samples for SCr measurement. Samples will be tested locally for the purposes of checking eligibility and assigning CKD stage.
- Blood samples for local laboratory evaluation (clinical chemistry and hematology); see [Table 2](#).
- Urine samples for local laboratory evaluation; see [Table 2](#).
- AEs and SAEs (from time of signing informed consent).

Patients must satisfy all the inclusion criteria and none of the exclusion criteria listed in Sections [7.2](#) and [7.3](#) and must provide signed and dated informed consent prior to entering the study. Patients who will undergo ORFM will provide specific written informed consent to undergo the procedure as part of the Screening Visit at the selected study centers.

.....

Now Reads:

A Screening visit will take place up to 7 days before a scheduled CT examination for post-EVAR surveillance. *Note that screening visit assessments may be conducted on the same day as baseline pre-scan assessments, dependent on the site's local laboratory turnaround time for SCr. In this instance assessments required for screening and baseline pre-scan need only be*

conducted once. If the screening and baseline assessments occur on separate days, the assessments need to be completed at each visit.

At the Screening visit, the following will be collected and/or performed:

- Written informed consent. *Note, the consent process may start prior to the Screening visit but the most current version of the consent form must be signed within 7 days prior to the baseline visit and prior to any screening assessments being conducted.*
- Demographic information.
- General medical/surgical history.
- Prior and concomitant medications.
- All female patients of child-bearing potential will undergo a urine pregnancy test.
- Physical examination.
- Vital signs (blood pressure, heart rate, respiration rate) in the sitting position.
- 12-lead electrocardiogram (ECG).
- Blood samples for SCr measurement. Samples will be tested locally for the purposes of checking eligibility and assigning CKD stage.
- Blood samples for local laboratory evaluation (clinical chemistry and hematology); see [Table 2](#).
- Urine samples for local laboratory evaluation; see [Table 2](#).
- *Pre-treatment* AEs and SAEs (from time of signing informed consent).

Patients must satisfy all the inclusion criteria and none of the exclusion criteria listed in Sections [7.2](#) and [7.3](#) and must provide signed and dated informed consent prior to entering the study. Patients who will undergo ORFM will provide specific written informed consent to undergo the procedure as part of the Screening Visit at the selected study centers *in the USA*.

.....

Section 9.2, Baseline Visit

Previously Read:

The Baseline visit will take place within 5 days of the Screening visit. Some procedures from the Screening Visit can be performed at the Baseline Visit for patient convenience; however,

informed consent must be obtained from 5 days prior and up to a minimum of 24 hours prior to the Baseline Visit.

At the Baseline Visit, the following will be collected and/or performed:

Before administration of Visipaque™ 320 mgI/mL or saline placebo the following will be collected and/or performed:

- All female patients of child-bearing potential will undergo a urine pregnancy test.
- Inclusion/exclusion criteria will be checked.
- Demographic information.
- General medical/surgical history.
- Prior and concomitant medication.
- Physical examination.
- Vital signs (blood pressure, heart rate, respiration rate) in the sitting position.
- The patient will be randomized to the CECT arm or NECT arm by IWRS/IVRS.
- Blood samples will be drawn for laboratory evaluation (local clinical chemistry and hematology if not already done at screening and for central determination of SCr, cystatin C and N-GAL); see [Table 2](#).
- Urine sample for clinical chemistry (if not already done at screening), and Nephrocheck® biomarkers (where local NephroCheck® testing is available).
- The patient will receive oral hydration (500 mL of water) following collection of blood samples for central analysis of SCr.
- AEs, SAEs and critical events, including EVAR-related post-baseline events.
- Optional ORFM; for a subset of patients at selected sites, MB-102 will be administered 1 hour prior to Visipaque™ or saline placebo.

Administration of Visipaque™ 320 mgI/mL or saline placebo:

- Patients in the CECT arm will receive 100 mL of Visipaque™ Injection 320 mg I/mL followed by a 10 mL saline flush.
- Patients in the NECT arm will receive 100 mL of saline placebo, followed by a 10 mL saline flush.

After administration of Visipaque™ 320 mgI/mL or saline placebo the following will be collected and/or performed:

- All patients will undergo a CT scan.
- Patients in the NECT arm will undergo non-contrast duplex ultrasonography after their nonenhanced CT scan, ideally on the same day as the NECT imaging and within 2 days of performing the NECT.
- Vital signs (blood pressure, heart rate, respiration rate) in the sitting position.
- All patients will be encouraged to drink at least 2500 mL of water in the 24 hours immediately following the CT scan. Patients in the NECT arm should start drinking the water after their ultrasonography, if it is performed on the same day as the NECT.
- AEs, SAEs and critical events, including EVAR-related post-baseline events.
- Urine samples for Nephrocheck® biomarkers (where local NephroCheck® testing is available) collected 4 hours post-CT.
- Optional ORFM; for a subset of patients at selected sites, monitoring of renal function will continue up to 4 hours post-CT.

See Section [10.2](#) and the Study Schedule of Events Table ([Table 1](#)) for further details.

Now Reads:

The Baseline visit will take place within 7 days of the Screening visit.

At the Baseline Visit, the following will be collected and/or performed:

Before administration of Visipaque™ 320 mgI/mL or saline placebo the following will be collected and/or performed:

- All female patients of child-bearing potential will undergo a urine pregnancy test.
- Inclusion/exclusion criteria will be checked.
- General medical/surgical history.
- Prior and concomitant medication.
- Physical examination.
- Vital signs (blood pressure, heart rate, respiration rate) in the sitting position.
- The patient will be randomized to the CECT arm or NECT arm by IWRS/IVRS.

- Blood samples will be drawn for laboratory evaluation (local clinical chemistry and hematology if not already done at screening and for central determination of SCr, cystatin C and N-GAL); see [Table 2](#).
- Urine sample for clinical chemistry (if not already done at screening), and Nephrocheck® biomarkers (where local NephroCheck® testing is available).
- The patient will receive oral hydration (500 mL of *fluids*) following collection of blood samples for central analysis of SCr. *In case of concern about the patient's compliance and/or capability to follow the oral hydration instructions, i.v. administration of isotonic crystalloid solution (saline or bicarbonate) may be considered. Decision on use of i.v. hydration will be made and documented before randomization (to be implemented regardless of whether the subject is randomized to the NECT or CECT arm).*
- *Pre-treatment* AEs, SAEs and critical events, including EVAR-related post-baseline events (*from time of signing informed consent*).
- Optional ORFM; for a subset of patients at selected sites, MB-102 will be administered 1 hour prior to Visipaque™ or saline placebo.

Administration of Visipaque™ 320 mgI/mL or saline placebo:

- Patients in the CECT arm will receive 100 mL of Visipaque™ Injection 320 mg I/mL followed by a 10 mL saline flush.
- Patients in the NECT arm will receive 100 mL of saline placebo, followed by a 10 mL saline flush.

After administration of Visipaque™ 320 mgI/mL or saline placebo the following will be collected and/or performed:

- All patients will undergo a CT scan.
- Patients in the NECT arm will undergo non-contrast duplex ultrasonography after their nonenhanced CT scan, ideally on the same day as the NECT imaging and within 2 days of performing the NECT.
- Vital signs (blood pressure, heart rate, respiration rate) in the sitting position.
- All patients will *need* to drink at least 2500 mL of *fluids* in the 24 hours immediately following the CT scan. Patients in the NECT arm should start drinking the *fluids* after their ultrasonography, if it is performed on the same day as the NECT. *In case of concern about the patient's compliance and/or capability to follow the oral hydration instructions, i.v. administration of isotonic crystalloid solution (saline or bicarbonate) may be considered. The total volume of fluid intake, in-clinic, will be documented.*

- *Treatment-emergent AEs, treatment-emergent SAEs and critical events, including EVAR-related post-baseline events.*
- Urine samples for Nephrocheck® biomarkers (where local NephroCheck® testing is available) collected 4 hours post-CT.
- Optional ORFM; for a subset of patients at selected sites *in the USA*, monitoring of renal function will continue up to 4 hours post-CT.
- *On discharge, patients will be instructed to continue with fluid consumption to ensure a total of 2500 mL over the 24 hours following the CT scan (NECT and CECT arms). Patients will be provided a card to document fluid consumption.*

See Section 10.2 and the Study Schedule of Events Table (Table 1) for further details.

Section 9.2.3, Optical Renal Function Monitoring, Second Paragraph, First Sentence

Previously Read:

A subset of patients (no more than 100), at selected sites, may be recruited in order to investigate this exploratory endpoint.

Now Reads:

A subset of patients (no more than 100), at selected sites *in the USA*, may be recruited in order to investigate this exploratory endpoint.

Section 9.3, Follow-Up 1, Bulleted List

Previously Read:

- Vital signs (blood pressure, heart rate, respiration rate) in the sitting position.
- Blood sample for SCr, cystatin C, N-GAL.
- Urine sample for Nephrocheck® biomarkers (where local NephroCheck® testing is available).
- Concomitant medication, AEs, SAEs and critical events including EVAR-related post-baseline events (collected by telephone call for patients receiving a home visit).

Now Reads:

- Vital signs (blood pressure, heart rate, respiration rate) in the sitting position.

- Blood sample for SCr, cystatin C, N-GAL. *Sampling for Follow-Up 1 should occur as close to 48 hours as possible to support the primary endpoint assessment for AKI [ACR 2015], with use of the -6 hour window being preferable to use of the +6 hour window.*
- Urine sample for Nephrocheck® biomarkers (where local NephroCheck® testing is available).
- Concomitant medication, AEs, SAEs and critical events including EVAR-related post-baseline events (collected by telephone call for patients receiving a home visit).
- *Collect patient card with fluid hydration volumes and check accuracy with the patient.*

Section 9.4, Follow-up 2, Third Bullet Point

Previously Read:

- Blood samples for SCr, cystatin C, and N-GAL (central laboratory analysis) and any additional local laboratory evaluation that the Investigator judges appropriate.

Now Reads:

- *Blood samples for SCr, cystatin C, and N-GAL (central laboratory analysis).*

Section 10.2.1, Clinical Laboratory Evaluation, Table 2, Clinical Laboratory Parameters, Fifth Column

The following text is deleted:

Local Laboratory:

Any additional local lab evaluation that the investigator judges appropriate.

Section 10.2.5, Critical Study Events

Previously Read:

Critical events (e.g., death, requirement for dialysis, hospitalization, EVAR-related post-baseline events etc.) will be documented and adjudicated according to the CEAC Charter.

Now Reads:

Critical events include, but are not limited to:

- *Death*
- *Major Adverse Renal Cardiac Event (MARCE)*
- *Renal replacement therapy (dialysis, hemofiltration/ultrafiltration, renal transplant)*
- *Hospitalization due to worsening renal impairment/renal failure*
- *EVAR-related post-baseline events*

Critical events will be *identified by the Investigator*, documented *in the CRF*, and adjudicated according to the CEAC Charter.

A critical event is expected to be associated with a reported AE or SAE. More than one critical event may be associated with the same AE or SAE and the terms reported for critical events and AEs/SAEs can differ. Refer to Section 10.2.6 for further information.

Section 10.2.6, Adverse Events, Laboratory AE Evaluation

Previously Read:

Interpretation and follow-up of abnormal laboratory test results should be conducted in consideration of the clinical situation of the patient. Any abnormal laboratory findings that constitute an AE should be reported as such and should be followed up until the outcome is known. Also, additional diagnostic tests may be indicated to determine a more precise diagnosis of the patient's condition (e.g., ordering a WBC differential to help characterize a high or low WBC count, or ordering a determination of red cell indices to help characterize a low hematocrit).

Now Reads:

Interpretation and follow-up of abnormal laboratory test results should be conducted in consideration of the clinical situation of the patient. Any abnormal laboratory findings that constitute an AE should be reported as such and should be followed up until the outcome is known. Also, additional diagnostic tests may be indicated to determine a more precise diagnosis of the patient's condition (e.g., ordering a WBC differential to help characterize a high or low WBC count, or ordering a determination of red cell indices to help characterize a low hematocrit).

To ensure a consistent approach, an AE/SAE should always be reported in the CRF for AKI if laboratory test results show a SCr increase of ≥ 0.3 mg/dL (≥ 26.4 $\mu\text{mol/L}$) or an increase to $\geq 150\%$ to 200% (≥ 1.5 to 2.0 fold) from baseline and/or the previous test result.

Section 10.2.7, Serious Adverse Events, Third Bullet Point**Previously Read:**

- Requires in-patient hospitalization or prolongation of existing hospitalization.

Now Reads:

- Requires in-patient hospitalization or prolongation of existing hospitalization.
Hospitalizations that are not due to, or associated with, an AE should not be reported as an SAE, e.g., pre-planned hospitalizations for diagnostic tests.

Section 12.3.3, Determination of Per Protocol Set, First Sentence**Previously Read:**

The per-protocol (PP) set will include all patients who receive Visipaque™ or saline placebo and have both baseline and post-scan SCr measurements.

Now Reads:

The per-protocol (PP) set will include all patients who receive Visipaque™ or saline placebo, have both baseline and post-scan SCr measurements, *and do not have any major protocol deviations with the potential of impacting data analyses and/or interpretability.*

Section 12.5, Study Treatments**Previously Read:**

For each administration of Visipaque or saline placebo, the volume administered will be summarized.

Now Reads:

For each administration of Visipaque or saline placebo, the volume administered will be summarized. *Additionally, hydration pre-scan and within 24 hours post-scan will be summarized in terms of oral, i.v., and total volume of fluids.*

Section 12.6.4, Supportive Analyses**Previously Read:**

In addition, the incidence rates for the 2 treatment groups stratified by CKD stage and the associated 95% CIs will also be reported. The primary analysis will be repeated in the PP set by CKD stage and for stage III/IV combined.

Now Reads:

The incidence rates for the 2 treatment groups stratified by CKD stage and the associated 95% CIs will also be reported. The primary analysis will be repeated in the PP set by CKD stage and for stage III/IV combined.

In addition, a sensitivity analysis will be performed in the FAS adjusting for the covariates of total fluid intake pre-scan and total fluid intake within 24 hours post-scan. This analysis will be done by CKD stage and for stage III/IV combined.

Section 12.7.1, Secondary Variables and Analyses, Other Secondary Endpoint Analyses, Fourth Bullet**Previously Read:**

- Incidence of requirement for renal replacement therapy (i.e., renal transplant, dialysis, or hemofiltration) assessed at 6 months (Follow-up 3).

Now Reads:

- Incidence of requirement for renal replacement therapy (i.e., renal transplant, dialysis, or hemofiltration/*ultrafiltration*) assessed at 6 months (Follow-up 3).

Section 14, References, New Reference Added

[\[ESC Guidelines 2014\]](#)

2014 ESC Guidelines on the diagnosis and treatment of aortic diseases. *European Heart Journal* 2014;35:2873–2926

16.2 Amendment A02

16.2.1 Reasons for Amendment

- Clarification of effective methods of contraception is added.
- Safety profile of Visipaque is clarified.

Where appropriate, the changes documented below are also made in the synopsis. Where appropriate the changes are indicated in *italics*.

16.2.2 Description of Changes

Section 6.3, Risks and Benefits to Patients, First Paragraph

Previously Read:

The potential risks for approved iodinated contrast agents are well known and have been detailed in American College of Radiology's Manual on Contrast Media [ACR 2015]. The majority of AEs related to contrast media are mild or moderate, non-life-threatening events. Serious acute contrast reactions are rare and have historically occurred in approximately 1 or 2 per 10,000 (0.01% to 0.02%) intravascular injections of low-osmolar contrast media [Katayama et al 1990]. For Visipaque™, the risks are also clearly described in the Investigator's Brochure (IB).

Now Reads:

The potential risks for approved iodinated contrast agents are well known and have been detailed in American College of Radiology's Manual on Contrast Media [ACR 2015]. The majority of AEs related to contrast media are mild or moderate, non-life-threatening events. Serious acute contrast reactions are rare and have historically occurred in approximately 1 or 2 per 10,000 (0.01% to 0.02%) intravascular injections of low-osmolar contrast media [Katayama et al 1990]. *Visipaque™ was approved in 1992 and has since been used in more than 115 million patients. In this phase 4 trial, Visipaque™ will be used in line with approved product information and* the risks are also clearly described in the Investigator's Brochure (IB).

Section 7.2, Inclusion Criteria

Previously Read:

Patients may be included in the study if they meet all of the following criteria:

- (1) Is ≥ 18 years of age at the time that written informed consent is obtained.

- (2) Is male or is a non-pregnant, non-lactating female who is either surgically sterile (has a documented bilateral tubal ligation or oophorectomy and/or documented hysterectomy) or is postmenopausal (cessation of menses for more than 1 year). Women of childbearing potential must use adequate contraception from Screening until 30 days after the Baseline Visit and must have a negative result for a urine human chorionic gonadotropin pregnancy test at the Baseline Visit.
- (3) Is an outpatient who has undergone successful EVAR and is scheduled for post-procedural imaging with CT.
- (4) Has previously completed his or her first post-EVAR surveillance CECT imaging examination (usually performed around 1-month).
- (5) Has a documented diagnosis of stage III or IV (defined as $30 \leq \text{estimated glomerular filtration rate (eGFR)} < 60 \text{ mL/min/1.73 m}^2$ and $15 \leq \text{eGFR} < 30 \text{ mL/min/1.73 m}^2$, respectively, according to the Modification of Diet in Renal Disease [MDRD] equation) CKD and stable renal function (last 2 SCr values within $\pm 0.5 \text{ mg/dL}$ of each other, with the most recent value within 7 days prior to the scheduled CT examination and the preceding value within 1 to 12 months before that).
- (6) Is able to provide written informed consent.
- (7) Is able and willing to comply with all study procedures as described in the protocol.

Now Reads:

Patients may be included in the study if they meet all of the following criteria:

- (1) Is ≥ 18 years of age at the time that written informed consent is obtained.
- (2) Is male or is a non-pregnant, non-lactating female who is either surgically sterile (has a documented bilateral tubal ligation or oophorectomy and/or documented hysterectomy) or is postmenopausal (cessation of menses for more than 1 year). Women of childbearing potential must use adequate contraception* from Screening until 30 days after the Baseline Visit and must have a negative result for a urine human chorionic gonadotropin pregnancy test at the Baseline Visit.
- (3) Is an outpatient who has undergone successful EVAR and is scheduled for post-procedural imaging with CT.
- (4) Has previously completed his or her first post-EVAR surveillance CECT imaging examination (usually performed around 1-month).
- (5) Has a documented diagnosis of stage III or IV (defined as $30 \leq \text{estimated glomerular filtration rate (eGFR)} < 60 \text{ mL/min/1.73 m}^2$ and $15 \leq \text{eGFR} < 30 \text{ mL/min/1.73 m}^2$, respectively, according to the Modification of Diet in Renal Disease [MDRD] equation) CKD and stable renal function (last 2 SCr values within $\pm 0.5 \text{ mg/dL}$ of each other, with

the most recent value within 7 days prior to the scheduled CT examination and the preceding value within 1 to 12 months before that).

- (6) Is able to provide written informed consent.
- (7) Is able and willing to comply with all study procedures as described in the protocol.

* *Adequate contraception is based on those methods identified in the Clinical Trial Facilitation Group (CTFG) document [CTFG Guidance 2014] for clarification of effective contraception. Such methods include: combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal); progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable); intrauterine device; intrauterine hormone-releasing system; bilateral tubal occlusion; vasectomized partner; sexual abstinence (refer to Section 8.6).*

Section 8.6, Contraception and Pregnancy Avoidance Procedure, New Section Added

Now reads:

Women of childbearing potential who are sexually active with a non-sterilized male partner and males who are sexually active with a partner of childbearing potential must use adequate contraception from Screening until 30 days after the Baseline Visit. A woman NOT of childbearing potential is defined as surgically sterile (has a documented bilateral tubal ligation or oophorectomy and/or documented hysterectomy) or postmenopausal (cessation of menses for more than 1 year).

An acceptable method of contraception is defined as one that has no higher than a 1% failure rate based on those methods identified in the CTFG document for clarification of effective contraception [CTFG Guidance 2014]. Such methods include:

- *combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation¹:*
 - *oral*
 - *intravaginal*
 - *transdermal*
- *progestogen-only hormonal contraception associated with inhibition of ovulation¹:*
 - *oral*
 - *injectable*
 - *implantable²*
- *intrauterine device²*

- *intrauterine hormone-releasing system*²
- *bilateral tubal occlusion*²
- *vasectomized partner*^{2,3}
- *sexual abstinence*⁴

Patients will be provided with information on acceptable methods of contraception as part of the subject informed consent process. Women of childbearing potential must have a negative result for a urine human chorionic gonadotropin pregnancy test at the Baseline Visit.

Section 14, References, Additional reference added

[CTFG Guidance 2014]

Clinical Trial Facilitation Group (CTFG) (2014) Recommendations related to contraception and pregnancy testing in clinical trials.

http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf. Accessed 06 December 2017.

Section 15.1, Information on Investigational and Registered Products

Previously read:

The reference document for this study is the current IB. The reference document provides up-to-date information on the efficacy and safety of Visipaque™ Injection 320 mg/mL and is used for assessing expectedness of Serious Adverse Drug Reactions (SADRs), in order to determine regulatory reportability. An unexpected ADR is a reaction whose nature, seriousness, severity, or outcome is not consistent with the applicable product information.

Now reads:

The reference document for this *phase 4 study in an approved indication and within boundaries of approved product information for Visipaque™* is the current IB. This reference document provides up-to-date information on the efficacy and safety of Visipaque™ Injection 320 mg/mL. *The safety profile of Visipaque™ is based on clinical and extensive postmarketing surveillance experience. Section 6.2.3.8 (Undesirable effects) of the IB will be used for* assessing expectedness of Serious Adverse Drug Reactions (SADRs), in order to determine regulatory reportability. An unexpected ADR is a reaction whose nature, seriousness, severity, or outcome is not consistent with the applicable product information.

16.3 Amendment A03

16.3.1 Reasons for Amendment

- Acceptable methods of contraception are 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 is increased from 24 hours to 48 hours in line with core safety information.
- Thyroid-stimulating hormone (TSH) is added to the Screening laboratory evaluation.

Where appropriate, the changes documented below are also made in the synopsis. Where appropriate the changes are indicated in *italics*.

16.3.2 Description of Changes

Section 7.2, Inclusion Criteria, Asterisked note to Inclusion Criterion 2

Previously Read:

- * Adequate contraception is based on those methods identified in the Clinical Trial Facilitation Group (CTFG) document [\[CTFG Guidance 2014\]](#) for clarification of effective contraception. Such methods include: combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal); progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable); intrauterine device; intrauterine hormone-releasing system; bilateral tubal occlusion; vasectomized partner; sexual abstinence (refer to Section 8.6).

Now Reads:

- * Adequate contraception is based on those methods identified in the Clinical Trial Facilitation Group (CTFG) document [\[CTFG Guidance 2014\]](#) for clarification of effective contraception. Such methods include: combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal); progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable); intrauterine device; intrauterine hormone-releasing system; bilateral tubal occlusion; vasectomized partner; sexual abstinence, *progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, male or female condom with or without spermicide cap, diaphragm or sponge with spermicide* (refer to Section 8.6).

Section 7.3, Exclusion Criteria, Exclusion Criterion 5**Previously Read:**

Is using metformin (e.g., Glucophage[®]) that cannot be discontinued for the period of 24 hours prior to the Baseline Visit and for at least 48 hours after the imaging procedure (renal function must be evaluated before metformin is resumed).

Now Reads:

Is using metformin (e.g., Glucophage[®]) that cannot be discontinued for the period of 48 hours prior to the Baseline Visit and for at least 48 hours after the imaging procedure (renal function must be evaluated before metformin is resumed).

Section 8.6,**Previously Read:**

Women of childbearing potential who are sexually active with a non-sterilized male partner and males who are sexually active with a partner of childbearing potential must use adequate contraception from Screening until 30 days after the Baseline Visit. A woman NOT of childbearing potential is defined as surgically sterile (has a documented bilateral tubal ligation or oophorectomy and/or documented hysterectomy) or postmenopausal (cessation of menses for more than 1 year).

An acceptable method of contraception is defined as one that has no higher than a 1% failure rate based on those methods identified in the CTFG document for clarification of effective contraception [CTFG Guidance 2014]. Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation¹:
 - oral
 - intravaginal
 - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation¹:
 - oral
 - injectable
 - implantable²
- intrauterine device²
- intrauterine hormone-releasing system²

- bilateral tubal occlusion²
- vasectomized partner^{2,3}
- sexual abstinence⁴

Patients will be provided with information on acceptable methods of contraception as part of the subject informed consent process. Women of childbearing potential must have a negative result for a urine human chorionic gonadotropin pregnancy test at the Baseline Visit.

¹ Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.

² Contraception methods that in the context of CTFG guidance are considered to have low user dependency.

³ Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success.

⁴ In the context of CTFG guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Now Reads:

Women of childbearing potential who are sexually active with a non-sterilized male partner and males who are sexually active with a partner of childbearing potential must use adequate contraception from Screening until 30 days after the Baseline Visit. A woman NOT of childbearing potential is defined as surgically sterile (has a documented bilateral tubal ligation or oophorectomy and/or documented hysterectomy) or postmenopausal (cessation of menses for more than 1 year).

Acceptable methods of contraception *that are considered as highly effective* are defined as *those with* no higher than a 1% failure rate based on those methods identified in the CTFG document for clarification of effective contraception [CTFG Guidance 2014]. Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation¹:
 - oral
 - intravaginal
 - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation¹:
 - oral
 - injectable

- implantable²
- intrauterine device²
- intrauterine hormone-releasing system²
- bilateral tubal occlusion²
- vasectomized partner^{2,3}
- sexual abstinence⁴

Acceptable, but not highly effective, birth control methods that result in a failure rate of more than 1% per year include:

- *progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action*
- *male or female condom with or without spermicide⁵*
- *cap, diaphragm or sponge with spermicide⁵*

Patients will be provided with information on acceptable methods of contraception as part of the subject informed consent process. Women of childbearing potential must have a negative result for a urine human chorionic gonadotropin pregnancy test at the Baseline Visit.

¹ Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.

² Contraception methods that in the context of CTFG guidance are considered to have low user dependency.

³ Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success.

⁴ In the context of CTFG guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

⁵ *A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.*

Section 9, Study Procedures, Table 1**Previously Read:****Table 1 Study Schedule of Events**

Parameter	Screening Visit (within -7 days) ^a	Baseline Visit			Follow-Up 1 (Baseline +48 hours ±6 hours) ^d	Follow-Up 2 (Baseline +7 days ±2 days) ^c	Follow-Up 3 (Baseline + 6 months ±2 weeks) ^d
		Pre-Scan ^a	Scan	Post Scan ^b			
Informed consent signed	X						
Inclusion/exclusion criteria	X ^a	X ^a					
Demographic information	X						
Medical/surgical history	X ^a	X ^a					
Prior/concomitant medication or procedures	X ^a	X ^a			X	X	X
Physical examination	X ^a	X ^a				X ^c	
Electrocardiogram (12-lead)	X						
Vital signs ^c	X ^a	X ^a		X	X	X ^c	
Pregnancy test (if indicated) ^f	X	X					
Randomization to CECT or NECT arm		X					
Blood and urine sampling for screening SCr, clinical chemistry, hematology, (local laboratory) ^g	X						
Blood sampling for SCr, cystatin C, and N-GAL (central laboratory) ^g		X			X	X ^c	X ^d
Urine sampling for NephroCheck® biomarkers (local laboratory, if available) ^g		X		X	X		
Adverse events	X	X		X	X	X	X
Serious adverse events and critical events as per CEAC ^h	X	X		X	X	X	X ^d
Hydration (500 mL) ⁱ		X					
ORFM (selected sites only)		X		X			
Saline administration (NECT arm only)			X				
Visipaque™ injection 320 mgI/mL administration (CECT arm only)			X				
CT scan ^j			X				
Non-contrast duplex ultrasonography (NECT arm only) ^k				X			
Reminder re: hydration (2500 mL) ⁱ				X			
Record hydration volume		X		X	X		

Table 1 Study Schedule of Events

Parameter	Screening Visit (within -7 days) ^a	Baseline Visit			Follow-Up 1 (Baseline +48 hours ±6 hours) ^d	Follow-Up 2 (Baseline +7 days ±2 days) ^e	Follow-Up 3 (Baseline + 6 months ±2 weeks) ^d
		Pre-Scan ^a	Scan	Post Scan ^b			

CEAC = Critical Events Adjudication Committee; CECT = contrast-enhanced computed tomography; NECT = nonenhanced computed tomography; ORFM = optical renal function monitor ; SCr = serum creatinine

^a Screening procedures may be conducted on the same day as baseline pre-scan assessments, dependent on the site's local laboratory turnaround time for Scr. In this instance assessments required for screening and baseline pre-scan need only be conducted once. If the screening and baseline assessments occur on separate days, the assessments need to be completed at each visit. A signed consent must be obtained from 7 days prior to the Baseline Visit and before any study screening or pre-scan assessments are conducted.

^b Within 4 hours after scanning.

^c If results obtained at Follow-Up 1 meet primary criteria (AKI stage ≥ 1 , per AKIN), Follow-Up 2 will be performed as a clinic visit. A telephone follow-up will be performed for all other patients. If the patient attends the clinic, the following will be performed: concomitant medication will be recorded, vital signs will be recorded, blood samples for clinical chemistry will be collected, physical examination, adverse events and critical events will be recorded. If the patient receives a telephone follow-up, the following will be recorded: concomitant medication, adverse events and critical events.

^d A blood sample for SCr will be collected either at the patient's home (if this service is locally available) or at the study center, and SAEs and critical events will be recorded either by telephone (for patients receiving a home visit) or at the study center.

^e Vital signs are to be measured in the sitting position. The patient should rest for at least 5 minutes before vital signs measurement.

^f If applicable, a negative urine pregnancy test must be obtained at the Screening and Baseline Visit for female patients.

^g All blood samples taken prior to dosing and following the scan will be taken from venous blood. Local laboratories will be used for determination of eligibility for the trial and for stratification during randomization. A central laboratory will be utilized for analysis of SCr, cystatin C, and N-GAL collected at the Baseline Visit, Follow-Up 1 and Follow-Up 2 (for patients meeting primary AKIN criteria at Follow-Up 1). Sampling for Follow-Up 1 should occur as close to 48 hours as possible to support the primary endpoint assessment for AKI [ACR 2015], with use of the -6 hour window being preferable to use of the +6 hour window. Urine samples collected for NephroCheck® biomarkers (TIMP-2 and IGFBP-7) for patients where local NephroCheck® testing is available will be taken just before the scan, 4 hours post scan, and at 48 hours post scan.

^h Critical events, including EVAR-related post-baseline events, will be collected from administration to approximately 6 months after administration of Visipaque™ Injection/ saline placebo for assessment by the CEAC.

ⁱ 500 mL of fluids after SCr sampling and before the CT scan to be consumed. 2500 mL of fluids within the 24 hours post-CT period to be consumed. In case of concern about the patient's compliance and/or capability to follow the oral hydration instructions, i.v. administration of isotonic crystalloid solution (saline or bicarbonate) may be considered. Decision on use of i.v. hydration to be made and documented prior to randomization and performed regardless of whether the patient is randomized to the NECT or CECT arm.

^j CT scan according to correct acquisition protocol.

^k Non-contrast duplex ultrasonography will be performed ideally on the same day as NECT imaging and within 2 days of performing the NECT according to correct acquisition protocol.

Now Reads:**Table 1 Study Schedule of Events**

Parameter	Screening Visit (within -7 days) ^a	Baseline Visit			Follow-Up 1 (Baseline +48 hours ±6 hours) ^d	Follow-Up 2 (Baseline +7 days ±2 days) ^c	Follow-Up 3 (Baseline + 6 months ±2 weeks) ^d
		Pre-Scan ^a	Scan	Post Scan ^b			
Informed consent signed	X						
Inclusion/exclusion criteria	X ^a	X ^a					
Demographic information	X						
Medical/surgical history	X ^a	X ^a					
Prior/concomitant medication or procedures	X ^a	X ^a			X	X	X
Physical examination	X ^a	X ^a				X ^c	
Electrocardiogram (12-lead)	X						
Vital signs ^c	X ^a	X ^a		X	X	X ^c	
Pregnancy test (if indicated) ^f	X	X					
Randomization to CECT or NECT arm		X					
Blood and urine sampling for screening SCr, clinical chemistry, hematology, <i>TSH</i> (local laboratory) ^g	X						
Blood sampling for SCr, cystatin C, and N-GAL (central laboratory) ^g		X			X	X ^c	X ^d
Urine sampling for NephroCheck® biomarkers (local laboratory, if available) ^g		X		X	X		
Adverse events	X	X		X	X	X	X
Serious adverse events and critical events as per CEAC ^h	X	X		X	X	X	X ^d
Hydration (500 mL) ⁱ		X					
ORFM (selected sites only)		X		X			
Saline administration (NECT arm only)			X				
Visipaque™ injection 320 mgI/mL administration (CECT arm only)			X				
CT scan ^j			X				
Non-contrast duplex ultrasonography (NECT arm only) ^k				X			
Reminder re: hydration (2500 mL) ⁱ				X			
Record hydration volume		X		X	X		

Table 1 Study Schedule of Events

Parameter	Screening Visit (within -7 days) ^a	Baseline Visit			Follow-Up 1 (Baseline +48 hours ±6 hours) ^d	Follow-Up 2 (Baseline +7 days ±2 days) ^e	Follow-Up 3 (Baseline + 6 months ±2 weeks) ^d
		Pre-Scan ^a	Scan	Post Scan ^b			

CEAC = Critical Events Adjudication Committee; CECT = contrast-enhanced computed tomography; NECT = nonenhanced computed tomography; ORFM = optical renal function monitor; SCr = serum creatinine; *TSH* = *Thyroid-stimulating hormone*

^a Screening procedures may be conducted on the same day as baseline pre-scan assessments, dependent on the site's local laboratory turnaround time for Scr. In this instance assessments required for screening and baseline pre-scan need only be conducted once. If the screening and baseline assessments occur on separate days, the assessments need to be completed at each visit. A signed consent must be obtained from 7 days prior to the Baseline Visit and before any study screening or pre-scan assessments are conducted.

^b Within 4 hours after scanning.

^c If results obtained at Follow-Up 1 meet primary criteria (AKI stage ≥ 1 , per AKIN), Follow-Up 2 will be performed as a clinic visit. A telephone follow-up will be performed for all other patients. If the patient attends the clinic, the following will be performed: concomitant medication will be recorded, vital signs will be recorded, blood samples for clinical chemistry will be collected, physical examination, adverse events and critical events will be recorded. If the patient receives a telephone follow-up, the following will be recorded: concomitant medication, adverse events and critical events.

^d A blood sample for SCr will be collected either at the patient's home (if this service is locally available) or at the study center, and SAEs and critical events will be recorded either by telephone (for patients receiving a home visit) or at the study center.

^e Vital signs are to be measured in the sitting position. The patient should rest for at least 5 minutes before vital signs measurement.

^f If applicable, a negative urine pregnancy test must be obtained at the Screening and Baseline Visit for female patients.

^g All blood samples taken prior to dosing and following the scan will be taken from venous blood. Local laboratories will be used for determination of eligibility for the trial and for stratification during randomization. A central laboratory will be utilized for analysis of SCr, cystatin C, and N-GAL collected at the Baseline Visit, Follow-Up 1 and Follow-Up 2 (for patients meeting primary AKIN criteria at Follow-Up 1). Sampling for Follow-Up 1 should occur as close to 48 hours as possible to support the primary endpoint assessment for AKI [ACR 2015], with use of the -6 hour window being preferable to use of the +6 hour window. Urine samples collected for NephroCheck® biomarkers (TIMP-2 and IGFBP-7) for patients where local NephroCheck® testing is available will be taken just before the scan, 4 hours post scan, and at 48 hours post scan.

^h Critical events, including EVAR-related post-baseline events, will be collected from administration to approximately 6 months after administration of Visipaque™ Injection/ saline placebo for assessment by the CEAC.

ⁱ 500 mL of fluids after SCr sampling and before the CT scan to be consumed. 2500 mL of fluids within the 24 hours post-CT period to be consumed. In case of concern about the patient's compliance and/or capability to follow the oral hydration instructions, i.v. administration of isotonic crystalloid solution (saline or bicarbonate) may be considered. Decision on use of i.v. hydration to be made and documented prior to randomization and performed regardless of whether the patient is randomized to the NECT or CECT arm.

^j CT scan according to correct acquisition protocol.

^k Non-contrast duplex ultrasonography will be performed ideally on the same day as NECT imaging and within 2 days of performing the NECT according to correct acquisition protocol.

Section 10.2.1, Clinical Laboratory Evaluation, Table 2**Previously Read:****Table 2 Clinical Laboratory Parameters**

Screening	Baseline	Baseline 4 hours post scan	Follow-Up 1 (48 hours ±6 hours)	Follow-Up 2 (7 days ±2 days)	Follow-Up 3 (6 months ±2 weeks)
<u>Local Laboratory:</u> <u>Clinical Chemistry:</u> Chloride Urea nitrogen Serum creatinine Bicarbonate Sodium Potassium Glucose Alkaline phosphatase Aspartate transaminase Alanine transaminase Bilirubin (Total) <u>Hematology:</u> Hematocrit Hemoglobin Platelet count White blood cell (WBC) count Lymphocyte % <u>Urinalysis (local lab):</u> Glucose Ketone Protein Blood <u>Pregnancy Test:</u> Urine dipstick	<u>Central Laboratory:</u> <u>Clinical Chemistry:</u> Serum creatinine Cystatin C Neutrophil gelatinase-associated lipocalin (N-GAL) <u>Local Laboratory:</u> <u>Urinalysis:</u> NephroCheck® biomarkers (TIMP-2, IGFBP-7) ^a <u>Pregnancy Test:</u> Urine dipstick	<u>Local Laboratory:</u> <u>Urinalysis:</u> NephroCheck® biomarkers (TIMP-2, IGFBP-7) ^a	<u>Central Laboratory:</u> <u>Clinical Chemistry:</u> Serum creatinine Cystatin C N-GAL <u>Local Laboratory:</u> <u>Urinalysis:</u> NephroCheck® biomarkers (TIMP-2, IGFBP-7) ^a	<u>Central Laboratory:</u> <u>Clinical Chemistry:</u> For patients having met the primary AKI criteria: Serum creatinine Cystatin C N-GAL	<u>Central Laboratory:</u> <u>Clinical Chemistry:</u> Serum creatinine

^a If local testing is available

Now Reads:**Table 2 Clinical Laboratory Parameters**

Screening	Baseline	Baseline 4 hours post scan	Follow-Up 1 (48 hours ±6 hours)	Follow-Up 2 (7 days ±2 days)	Follow-Up 3 (6 months ±2 weeks)
<u>Local Laboratory:</u> <u>Clinical Chemistry:</u> Chloride Urea nitrogen Serum creatinine Bicarbonate Sodium Potassium Glucose Alkaline phosphatase Aspartate transaminase Alanine transaminase Bilirubin (Total) <i>Thyroid-stimulating hormone^a</i> <u>Hematology:</u> Hematocrit Hemoglobin Platelet count White blood cell (WBC) count Lymphocyte % <u>Urinalysis (local lab):</u> Glucose Ketone Protein Blood Pregnancy Test: Urine dipstick	<u>Central Laboratory:</u> <u>Clinical Chemistry:</u> Serum creatinine Cystatin C Neutrophil gelatinase-associated lipocalin (N-GAL) <u>Local Laboratory:</u> <u>Urinalysis:</u> NephroCheck® biomarkers (TIMP-2, IGFBP-7) ^b Pregnancy Test: Urine dipstick	<u>Local Laboratory:</u> <u>Urinalysis:</u> NephroCheck® biomarkers (TIMP-2, IGFBP-7) ^b	<u>Central Laboratory:</u> <u>Clinical Chemistry:</u> Serum creatinine Cystatin C N-GAL <u>Local Laboratory:</u> <u>Urinalysis:</u> NephroCheck® biomarkers (TIMP-2, IGFBP-7) ^b	<u>Central Laboratory:</u> <u>Clinical Chemistry:</u> For patients having met the primary AKI criteria: Serum creatinine Cystatin C N-GAL	<u>Central Laboratory:</u> <u>Clinical Chemistry:</u> Serum creatinine

^a supersensitive TSH (sTSH) assay if locally available^b If local testing is available

16.4 Amendment A04

16.4.1 Reasons for Amendment

- Potentially eligible subjects can enter this study any time during their post-EVAR follow-up, once they have passed the first imaging examination (commonly scheduled 1 month after the index EVAR), and if no complications, such as endoleaks, have been detected. Consequently, assessment for eligibility can happen years after the index EVAR, when documentation of the first imaging exam may not be available, despite subsequent follow-up examination(s) providing sufficient assurance on the stable post-EVAR status of such patients. The changes in inclusion criteria #3 and 4 and exclusion criterion #2 aim to allow enrolment of otherwise eligible post-EVAR patients in cases where documentation and evidence on the first month imaging examination are not available. The requirement for stable post-EVAR conditions (no endoleak, no clinically meaningful EVAR-related complication) is unchanged, so the characteristics of the patient population remains unchanged.
- The screening period is increased from 7 days to 14 days for logistical reasons.
- Recent literature reference (McDonald et al. 2017) added.
- A definition of the end of the study is added.
- Clarification that randomization is in a 1:1 ratio.
- Text added to clarify that the use of N-acetylcysteine is 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 patients have been enrolled is increased from within 3 months to within 6 months of initiation.
- Clarification that ‘personnel who are 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’ is added to Section 9.2.

Where appropriate, the changes documented below are also made in the synopsis. Where appropriate the changes are indicated in *italics*.

16.4.2 Description of Changes

Section 4, Background Information and Study Rationale, Seventh Paragraph

Previously read:

Four large retrospective studies in which subjects were matched or stratified by propensity score have recently been published. Two studies by Davenport et al [Davenport et al 2013a] [Davenport et al 2013b] found i.v. low-osmolar and iso-osmolar contrast medium to be an independent risk factor for nephrotoxicity in patients with severe chronic renal impairment (the risk of nephrotoxicity increased progressively as renal function declined). The other 2 studies by McDonald et al [McDonald et al 2013b] [McDonald et al 2015] concluded that i.v. low-osmolar or iso-osmolar contrast medium may not be the causative agent in diminished renal function after contrast medium i.v. administration.

Now reads:

Four large retrospective studies in which subjects were matched or stratified by propensity score have recently been published. Two studies by Davenport et al [Davenport et al 2013a] [Davenport et al 2013b] found i.v. low-osmolar and iso-osmolar contrast medium to be an independent risk factor for nephrotoxicity in patients with severe chronic renal impairment (the risk of nephrotoxicity increased progressively as renal function declined). The other 2 studies by McDonald et al [McDonald et al 2013b] [McDonald et al 2015] concluded that i.v. low-osmolar or iso-osmolar contrast medium may not be the causative agent in diminished renal function after contrast medium i.v. administration. *More specifically, among patients at the highest perceived risk of post contrast AKI (throughout the entire spectrum of CKD, including stages III-V), i.v. administration of iodixanol for CECT was not an independent risk factor for AKI, dialysis, or mortality [McDonald et al. 2017].*

Section 6.1, Overall Study Design and Plan, Second Paragraph

Previously read:

The patients will be randomly assigned to undergo either CECT or NECT for this routine surveillance CT examination (full details are provided in the CT Imaging Manual). Patients in the CECT arm will receive a 100-mL i.v. injection of iodixanol (Visipaque Injection 320 mg I/mL), followed by a 10 mL saline flush, for enhancement of the CT examination. Patients in the NECT arm will receive a volume-matched i.v. injection of a saline placebo, followed by a 10 mL saline flush, before their CT examination. All patients (CECT and NECT arms) will be required to drink 500 mL of fluids following collection of blood samples for central analysis of SCr and prior to scanning. All patients (CECT and NECT arm) will be required to drink at least 2500 mL of fluids in the 24 hours immediately following CT scanning. To ensure a consistent approach, oral hydration is preferred, however, in case of concern about the patient's compliance and/or capability to follow the oral hydration instructions, i.v. administration of isotonic crystalloid solution (saline or bicarbonate) may be considered. In case of i.v. administration of crystalloids, the combination of oral and i.v. fluids

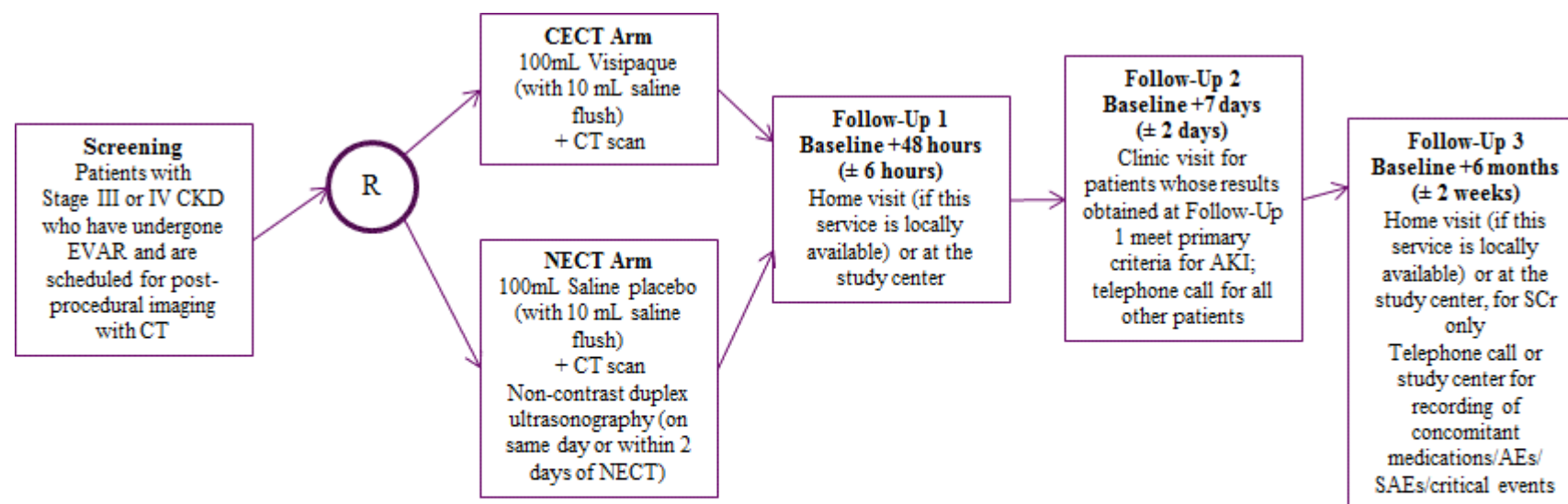
must equal a minimum of 500 mL pre-contrast material administration and 2500 mL within 24 hours post-contrast material administration. Subjects will be asked to record their fluid intake. The volume of fluids, before and within 24 hours after administration, must be carefully documented in source records and in the CRF. Decision on use of i.v. hydration will be made and documented before randomization and implemented regardless of whether the subject is randomized to the NECT or CECT arm.

Now reads:

The patients will be randomly assigned *in a 1:1 ratio* to undergo either CECT or NECT for this routine surveillance CT examination (full details are provided in the CT Imaging Manual). Patients in the CECT arm will receive a 100-mL i.v. injection of iodixanol (Visipaque Injection 320 mg I/mL), followed by a 10 mL saline flush, for enhancement of the CT examination. Patients in the NECT arm will receive a volume-matched i.v. injection of a saline placebo, followed by a 10 mL saline flush, before their CT examination. All patients (CECT and NECT arms) will be required to drink 500 mL of fluids following collection of blood samples for central analysis of SCr and prior to scanning. All patients (CECT and NECT arm) will be required to drink at least 2500 mL of fluids in the 24 hours immediately following CT scanning. To ensure a consistent approach, oral hydration is preferred, however, in case of concern about the patient's compliance and/or capability to follow the oral hydration instructions, i.v. administration of isotonic crystalloid solution (saline or bicarbonate) may be considered. In case of i.v. administration of crystalloids, the combination of oral and i.v. fluids must equal a minimum of 500 mL pre-contrast material administration and 2500 mL within 24 hours post-contrast material administration. Subjects will be asked to record their fluid intake. The volume of fluids, before and within 24 hours after administration, must be carefully documented in source records and in the CRF. Decision on use of i.v. hydration will be made and documented before randomization and implemented regardless of whether the subject is randomized to the NECT or CECT arm. *The use of N-acetylcysteine (NAC) is discouraged for the purpose of preventing AKI.*

Section 6.1, Figure 1, Study Diagram

Previously read:



AKI = Acute kidney injury

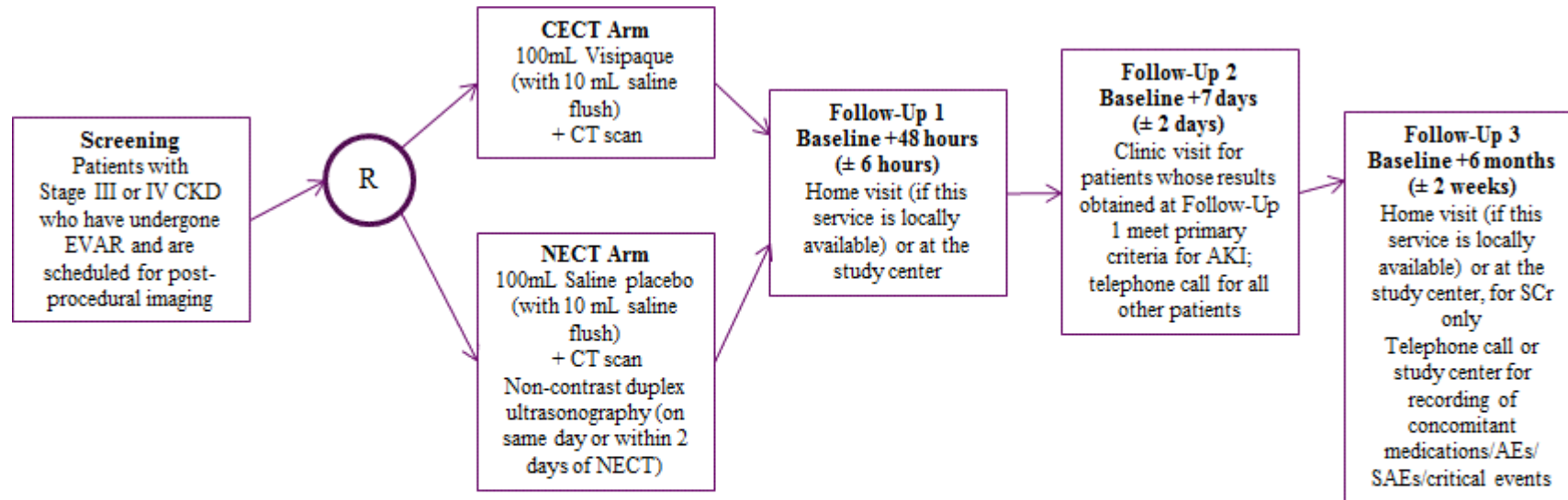
CECT = Contrast-enhanced computed tomography

CKD = Chronic kidney disease

EVAR = Endovascular aneurysm repair

NECT = Non-enhanced computed tomography

R = Randomization

Now reads:

AKI = Acute kidney injury
 CECT = Contrast-enhanced computed tomography
 CKD = Chronic kidney disease
 EVAR = Endovascular aneurysm repair
 NECT = Non-enhanced computed tomography
 R = Randomization

Section 6.2, Study Timeframe**Previously read:**

Patient recruitment is planned to start in the first half of 2017.

The expected duration of the study is approximately 2 years.

Now reads:

Patient recruitment is planned to start in the first half of 2017.

The expected duration of the study is approximately 2 years.

The end of the study is defined as the date of the last visit of the last subject in the study.

Section 7.2, Inclusion Criteria, Inclusion Criteria 3, 4, and 5**Previously read:**

- (3) Is an outpatient who has undergone successful EVAR and is scheduled for post-procedural imaging with CT.
- (4) Has previously completed his or her first post-EVAR surveillance CECT imaging examination (usually performed around 1-month).
- (5) Has a documented diagnosis of stage III or IV (defined as $30 \leq$ estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² and $15 \leq$ eGFR <30 mL/min/1.73 m², respectively, according to the Modification of Diet in Renal Disease [MDRD] equation) CKD and stable renal function (last 2 SCr values within ± 0.5 mg/dL of each other, with the most recent value within 7 days prior to the scheduled CT examination and the preceding value within 1 to 12 months before that).

Now reads:

- (3) Is an outpatient who has undergone successful EVAR and is scheduled for *his/her next* post-procedural imaging *follow-up examination*.
- (4) Has previously completed *one or more of* his or her post-EVAR surveillance imaging examination(s), *that provided evidence on stable post-EVAR status*.
- (5) Has a documented diagnosis of stage III or IV (defined as $30 \leq$ estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² and $15 \leq$ eGFR <30 mL/min/1.73 m², respectively, according to the Modification of Diet in Renal Disease [MDRD] equation) CKD and stable renal function (last 2 SCr values within ± 0.5 mg/dL of each other, with the most recent value within *14* days prior to the scheduled CT examination and the preceding value within 1 to 12 months before that).

Section 7.3, Exclusion Criteria, Exclusion Criterion 2**Previously read:**

- (2) Is a patient for whom an endoleak has already been discovered.

Now reads:

- (2) Is a patient for whom an endoleak *or other clinically meaningful EVAR-related complication (as judged by the investigator)* has already been discovered.

Section 7.3, Exclusion Criteria, Exclusion Criterion 6**Previously read:**

- (6) Has been exposed to any intravascular iodinated contrast medium in the 7 days prior to the Baseline Visit.

Now reads:

- (6) Has been exposed to any intravascular iodinated contrast medium in the *14* days prior to the Baseline Visit.

Section 7.4.2, Study or Site Termination**Previously read:**

The Sponsor reserves the right to terminate the study at any time. The Sponsor also reserves the right to discontinue participation of a study center at which no patients have been enrolled within 3 months of initiation or in case of safety concerns or major protocol violations.

Now reads:

The Sponsor reserves the right to terminate the study at any time. The Sponsor also reserves the right to discontinue participation of a study center at which no patients have been enrolled within 6 months of initiation or in case of safety concerns or major protocol violations.

Section 8.2, Method of Numbering Patients and Assigning Patients to Treatment Groups, Fourth Paragraph**Previously read:**

Once patients have completed the screening process they will be enrolled in the study and will be randomly assigned to the NECT group or the CECT group in accordance with a pre-specified randomization list. Allocation to the enrolment groups, including randomization, will be performed centrally (via the IWRS or IVRS) by the Sponsor or contract research organization (CRO). Randomization will be stratified by CKD stage to achieve a balance of this factor between treatment groups.

Now reads:

Once patients have completed the screening process they will be enrolled in the study and will be randomly assigned to the NECT group or the CECT group *in a 1:1 ratio* in accordance with a pre-specified randomization list. Allocation to the enrolment groups, including randomization, will be performed centrally (via the IWRS or IVRS) by the Sponsor or contract research organization (CRO). Randomization will be stratified by CKD stage to achieve a balance of this factor between treatment groups.

Section 8.5, Prior and Concurrent Medications or Procedures, Second Paragraph**Previously read:**

Metformin, NSAIDs, and drugs with nephrotoxic potential will be required to be discontinued temporarily per exclusion criteria #5 and #15, and the current use of i.v. vasopressor or inotropic medications is prohibited per exclusion criterion #14. The prophylactic use of acetylsalicylic acid (Aspirin) in a dose of ≤ 100 mg QD is permitted.

Now reads:

Metformin, NSAIDs, and drugs with nephrotoxic potential will be required to be discontinued temporarily per exclusion criteria #5 and #15, and the current use of i.v. vasopressor or inotropic medications is prohibited per exclusion criterion #14. The prophylactic use of acetylsalicylic acid (Aspirin) in a dose of ≤ 100 mg QD is permitted. *The use of N-acetylcysteine (NAC) is discouraged for the purpose of preventing AKI.*

Section 9, Study Procedures, Table 1**Previously read:****Table 1 Study Schedule of Events**

Parameter	Screening Visit (within -7 days) ^a	Baseline Visit			Follow-Up 1 (Baseline +48 hours ±6 hours) ^d	Follow-Up 2 (Baseline +7 days ±2 days) ^c	Follow-Up 3 (Baseline + 6 months ±2 weeks) ^d
		Pre-Scan ^a	Scan	Post Scan ^b			
Informed consent signed	X						
Inclusion/exclusion criteria	X ^a	X ^a					
Demographic information	X						
Medical/surgical history	X ^a	X ^a					
Prior/concomitant medication or procedures	X ^a	X ^a			X	X	X
Physical examination	X ^a	X ^a				X ^c	
Electrocardiogram (12-lead)	X						
Vital signs ^e	X ^a	X ^a		X	X	X ^c	
Pregnancy test (if indicated) ^f	X	X					
Randomization to CECT or NECT arm		X					
Blood and urine sampling for screening SCr, clinical chemistry, hematology, TSH (local laboratory) ^g	X						
Blood sampling for SCr, cystatin C, and N-GAL (central laboratory) ^g		X			X	X ^c	X ^d
Urine sampling for NephroCheck® biomarkers (local laboratory, if available) ^g		X		X	X		
Adverse events	X	X		X	X	X	X
Serious adverse events and critical events as per CEAC ^h	X	X		X	X	X	X ^d
Hydration (500 mL) ⁱ		X					
ORFM (selected sites only)		X		X			
Saline administration (NECT arm only)			X				
Visipaque™ injection 320 mgI/mL administration (CECT arm only)			X				
CT scan ^j			X				
Non-contrast duplex ultrasonography (NECT arm only) ^k				X			
Reminder re: hydration (2500 mL) ⁱ				X			
Record hydration volume		X		X	X		

Table 1 Study Schedule of Events

Parameter	Screening Visit (within -7 days) ^a	Baseline Visit			Follow-Up 1 (Baseline +48 hours ±6 hours) ^d	Follow-Up 2 (Baseline +7 days ±2 days) ^c	Follow-Up 3 (Baseline + 6 months ±2 weeks) ^d
		Pre-Scan ^a	Scan	Post Scan ^b			

CEAC = Critical Events Adjudication Committee; CECT = contrast-enhanced computed tomography; NECT = nonenhanced computed tomography; ORFM = optical renal function monitor; SCr = serum creatinine; TSH = Thyroid-stimulating hormone

^a Screening procedures may be conducted on the same day as baseline pre-scan assessments, dependent on the site's local laboratory turnaround time for Scr. In this instance assessments required for screening and baseline pre-scan need only be conducted once. If the screening and baseline assessments occur on separate days, the assessments need to be completed at each visit. A signed consent must be obtained from 7 days prior to the Baseline Visit and before any study screening or pre-scan assessments are conducted.

^b Within 4 hours after scanning.

^c If results obtained at Follow-Up 1 meet primary criteria (AKI stage ≥1, per AKIN), Follow-Up 2 will be performed as a clinic visit. A telephone follow-up will be performed for all other patients. If the patient attends the clinic, the following will be performed: concomitant medication will be recorded, vital signs will be recorded, blood samples for clinical chemistry will be collected, physical examination, adverse events and critical events will be recorded. If the patient receives a telephone follow-up, the following will be recorded: concomitant medication, adverse events and critical events.

^d A blood sample for SCr will be collected either at the patient's home (if this service is locally available) or at the study center, and SAEs and critical events will be recorded either by telephone (for patients receiving a home visit) or at the study center.

^e Vital signs are to be measured in the sitting position. The patient should rest for at least 5 minutes before vital signs measurement.

^f If applicable, a negative urine pregnancy test must be obtained at the Screening and Baseline Visit for female patients.

^g All blood samples taken prior to dosing and following the scan will be taken from venous blood. Local laboratories will be used for determination of eligibility for the trial and for stratification during randomization. A central laboratory will be utilized for analysis of SCr, cystatin C, and N-GAL collected at the Baseline Visit, Follow-Up 1 and Follow-Up 2 (for patients meeting primary AKIN criteria at Follow-Up 1). Sampling for Follow-Up 1 should occur as close to 48 hours as possible to support the primary endpoint assessment for AKI [ACR 2015], with use of the -6 hour window being preferable to use of the +6 hour window. Urine samples collected for NephroCheck® biomarkers (TIMP-2 and IGFBP-7) for patients where local NephroCheck® testing is available will be taken just before the scan, 4 hours post scan, and at 48 hours post scan.

^h Critical events, including EVAR-related post-baseline events, will be collected from administration to approximately 6 months after administration of Visipaque™ Injection/ saline placebo for assessment by the CEAC.

ⁱ 500 mL of fluids after SCr sampling and before the CT scan to be consumed. 2500 mL of fluids within the 24 hours post-CT period to be consumed. In case of concern about the patient's compliance and/or capability to follow the oral hydration instructions, i.v. administration of isotonic crystalloid solution (saline or bicarbonate) may be considered. Decision on use of i.v. hydration to be made and documented prior to randomization and performed regardless of whether the patient is randomized to the NECT or CECT arm.

^j CT scan according to correct acquisition protocol.

^k Non-contrast duplex ultrasonography will be performed ideally on the same day as NECT imaging and within 2 days of performing the NECT according to correct acquisition protocol.

Now reads:

Table 1 Study Schedule of Events

Parameter	Screening Visit (within -14 days) ^a	Baseline Visit			Follow-Up 1 (Baseline +48 hours ±6 hours) ^d	Follow-Up 2 (Baseline +7 days ±2 days) ^c	Follow-Up 3 (Baseline + 6 months ±2 weeks) ^d
		Pre-Scan ^a	Scan	Post Scan ^b			
Informed consent signed	X						
Inclusion/exclusion criteria	X ^a	X ^a					
Demographic information	X						
Medical/surgical history	X ^a	X ^a					
Prior/concomitant medication or procedures	X ^a	X ^a			X	X	X
Physical examination	X ^a	X ^a				X ^c	
Electrocardiogram (12-lead)	X						
Vital signs ^e	X ^a	X ^a		X	X	X ^c	
Pregnancy test (if indicated) ^f	X ^a	X ^a					
Randomization to CECT or NECT arm		X					
Blood and urine sampling for screening SCr, clinical chemistry, hematology, TSH (local laboratory) ^g	X						
Blood sampling for SCr, cystatin C, and N-GAL (central laboratory) ^g		X			X	X ^c	X ^d
Urine sampling for NephroCheck® biomarkers (local laboratory, if available) ^g		X		X	X		
Adverse events	X	X		X	X	X	X
Serious adverse events and critical events as per CEAC ^h	X	X		X	X	X	X ^d
Hydration (500 mL) ⁱ		X					
ORFM (selected sites only)		X		X			
Saline administration (NECT arm only)			X				
Visipaque™ injection 320 mgI/mL administration (CECT arm only)			X				
CT scan ^j			X				
Non-contrast duplex ultrasonography (NECT arm only) ^k				X			
Reminder re: hydration (2500 mL) ⁱ				X			
Record hydration volume		X		X	X		

Table 1 Study Schedule of Events

Parameter	Screening Visit (within -14 days) ^a	Baseline Visit			Follow-Up 1 (Baseline +48 hours ±6 hours) ^d	Follow-Up 2 (Baseline +7 days ±2 days) ^e	Follow-Up 3 (Baseline + 6 months ±2 weeks) ^d
		Pre-Scan ^a	Scan	Post Scan ^b			

CEAC = Critical Events Adjudication Committee; CECT = contrast-enhanced computed tomography; NECT = nonenhanced computed tomography; ORFM = optical renal function monitor; SCr = serum creatinine; TSH = Thyroid-stimulating hormone

^a Screening procedures may be conducted on the same day as baseline pre-scan assessments, dependent on the site's local laboratory turnaround time for SCr. **In this instance assessments required for screening and baseline pre-scan need only be conducted once. If the screening and baseline assessments occur on separate days, the assessments need to be completed at each visit.** A signed consent must be obtained from 14 days prior to the Baseline Visit and before any study screening or pre-scan assessments are conducted.

^b Within 4 hours after scanning.

^c If results obtained at Follow-Up 1 meet primary criteria (AKI stage ≥1, per AKIN), Follow-Up 2 will be performed as a clinic visit. A telephone follow-up will be performed for all other patients. If the patient attends the clinic, the following will be performed: concomitant medication will be recorded, vital signs will be recorded, blood samples for clinical chemistry will be collected, physical examination, adverse events and critical events will be recorded. If the patient receives a telephone follow-up, the following will be recorded: concomitant medication, adverse events and critical events.

^d A blood sample for SCr will be collected either at the patient's home (if this service is locally available) or at the study center, and SAEs and critical events will be recorded either by telephone (for patients receiving a home visit) or at the study center.

^e Vital signs are to be measured in the sitting position. The patient should rest for at least 5 minutes before vital signs measurement.

^f If applicable, a negative urine pregnancy test must be obtained at the Screening and Baseline Visit for female patients.

^g All blood samples taken prior to dosing and following the scan will be taken from venous blood. Local laboratories will be used for determination of eligibility for the trial and for stratification during randomization. A central laboratory will be utilized for analysis of SCr, cystatin C, and N-GAL collected at the Baseline Visit, Follow-Up 1 and Follow-Up 2 (for patients meeting primary AKIN criteria at Follow-Up 1). Sampling for Follow-Up 1 should occur as close to 48 hours as possible to support the primary endpoint assessment for AKI [ACR 2015], with use of the -6 hour window being preferable to use of the +6 hour window. Urine samples collected for NephroCheck® biomarkers (TIMP-2 and IGFBP-7) for patients where local NephroCheck® testing is available will be taken just before the scan, 4 hours post scan, and at 48 hours post scan.

^h Critical events, including EVAR-related post-baseline events, will be collected from administration to approximately 6 months after administration of Visipaque™ Injection/ saline placebo for assessment by the CEAC.

ⁱ 500 mL of fluids after SCr sampling and before the CT scan to be consumed. 2500 mL of fluids within the 24 hours post-CT period to be consumed. In case of concern about the patient's compliance and/or capability to follow the oral hydration instructions, i.v. administration of isotonic crystalloid solution (saline or bicarbonate) may be considered. Decision on use of i.v. hydration to be made and documented prior to randomization and performed regardless of whether the patient is randomized to the NECT or CECT arm.

^j CT scan according to correct acquisition protocol.

^k Non-contrast duplex ultrasonography will be performed ideally on the same day as NECT imaging and within 2 days of performing the NECT according to correct acquisition protocol.

Section 9.1, Screening Visit, Text from first paragraph to end of first bullet point**Previously read:**

A Screening visit will take place up to 7 days before a scheduled CT examination for post-EVAR surveillance. Note that screening visit assessments may be conducted on the same day as baseline pre-scan assessments, dependent on the site's local laboratory turnaround time for SCr. In this instance assessments required for screening and baseline pre-scan need only be conducted once. If the screening and baseline assessments occur on separate days, the assessments need to be completed at each visit.

At the Screening visit, the following will be collected and/or performed:

- Written informed consent. *Note, the consent process may start prior to the Screening visit but the most current version of the consent form must be signed within 7 days prior to the baseline visit and prior to any screening assessments being conducted.*

Now reads:

A Screening visit will take place up to 14 days before a scheduled CT examination for post-EVAR surveillance. Note that screening visit assessments may be conducted on the same day as baseline pre-scan assessments, dependent on the site's local laboratory turnaround time for SCr. In this instance assessments required for screening and baseline pre-scan need only be conducted once. If the screening and baseline assessments occur on separate days, the assessments need to be completed at each visit.

At the Screening visit, the following will be collected and/or performed:

- Written informed consent. *Note, the consent process may start prior to the Screening visit but the most current version of the consent form must be signed within 14 days prior to the baseline visit and prior to any screening assessments being conducted.*

Section 9.2, Baseline Visit, First Sentence**Previously read:**

The Baseline visit will take place within 7 days of the Screening visit.

Now reads:

The Baseline visit will take place within 14 days of the Screening visit.

Section 9.2, Baseline Visit, Administration of Visipaque™ 320 mgI/mL or saline placebo**Previously read:**

- Patients in the CECT arm will receive 100 mL of Visipaque™ Injection 320 mg I/mL followed by a 10 mL saline flush.
- Patients in the NECT arm will receive 100 mL of saline placebo, followed by a 10 mL saline flush.

Now reads:

- Patients in the CECT arm will receive 100 mL of Visipaque™ Injection 320 mg I/mL followed by a 10 mL saline flush.
- Patients in the NECT arm will receive 100 mL of saline placebo, followed by a 10 mL saline flush.
- *Study personnel must remain vigilant for the occurrence of AEs, particularly those that may be life-threatening. Personnel who are 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.*

Section 14, References, New reference added

[\[McDonald et al. 2017\]](#)

McDonald JS, McDonald RJ, Williamson EE, Kallmes DF. Is Intravenous Administration of Iodixanol Associated with Increased Risk of Acute Kidney Injury, Dialysis, or Mortality? A Propensity Score-adjusted Study. *Radiology*. 2017;285(2):414-424.

SIGNATURE PAGE

Date / Name	Justification / Role
Signed [REDACTED] Date of signature: 28-Mar-2018 15:32:09 GMT+0000	Justification: Approved Role: Head of Biometrics
Signed [REDACTED] Date of signature: 28-Mar-2018 16:49:31 GMT+0000	Justification: Approved Role: Head of Clinical Development